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Cancer Risk from Exposure to Plutonium and Uranium

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CONTENTS

CANCER RISK FROM EXPOSURE TO PLUTONIUM AND URANIUM

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Abstract-The objective of this publication is to provide a detailed review of results from recent epidemiological studies of cancer risk from exposure to plutonium and uranium, and how these results relate to the assumptions currently used for protection against alpha radiation. For plutonium, the two main studies are of the cohorts of workers employed at the nuclear installations at Mayak in the Russian Federation and at Sellafield in the United Kingdom. The analysis of the Mayak cohort provides an estimate of the slope of the dose-response for lung cancer risk, while at lower levels of plutonium exposure, the Sellafield cohort provides results that, within relatively large confidence intervals, are consistent with those for the Mayak cohort. Results from the Mayak cohort also show an association between plutonium exposure and risks of liver and bone cancers, but not of leukaemia. Lifetime excess risk of lung cancer mortality has been calculated for scenarios of acute and chronic inhalation of plutonium nitrate and plutonium oxide, similarly to that done previously for radon and its decay products in *Publication 115*. Estimated lifetime excess risks of lung cancer mortality per unit absorbed dose are close to those derived from miner studies for exposure to radon and its progeny, and are compatible with the assumption of a radiation weighting factor of 20 for alpha particles. Epidemiological studies of cancer risk associated with uranium exposure have been conducted among cohorts of European and North American workers involved in the nuclear fuel cycle. Current results do not allow the reliable derivation of dose-risk models for uranium for any cancer type. Continuation of efforts to improve dose assessment associated with uranium and plutonium exposure is recommended for future research.

Keywords: Uranium, Plutonium, Alpha emitter, Epidemiology, Cancer, Health Risk

MAIN POINTS

- **This report complements the review of risk from exposure to radon and its decay products given in *Publication 115*.**

- **Epidemiological studies of uranium exposure remain insufficient to provide reliable estimates of risk due to limits in dose reconstruction.**

- **For plutonium, the cohorts of workers from Mayak in the Russian Federation and from Sellafield in the United Kingdom provide quantitative information on lung cancer risk, the Mayak cohort also indicating associations with liver and bone cancer risks, but not with leukaemia risk.**

- **The lifetime excess risk of lung cancer mortality per unit absorbed dose to the lung attributable to acute and chronic exposures to plutonium nitrate and oxide varies between 1.4 and 1.7 per 10,000 individuals per mGy. These values are similar to those derived from miner studies for exposure to radon and its progeny.**

- **Comparing the lifetime excess risks of lung cancer mortality calculated for plutonium and radon progeny exposures with those from external gamma irradiation suggests a biological effectiveness of alpha particles relative to high energy photons that is compatible with the radiation weighting factor (w_R) of 20 assumed for alpha particles.**

EXECUTIVE SUMMARY

1. Objectives

(a) In the current radiological protection system, estimation of radiation risk and detriment is primarily based on the risks observed in the Life Span Study cohort of the Japanese atomic-bomb survivors, who were exposed at a high dose rate, mainly to gamma rays. It is assumed that these observed risk estimates can also be applied to different situations of exposure, such as internal contamination by radionuclides emitting alpha radiation, leading to protracted and heterogeneous irradiation, once account is taken of the relative biological effectiveness values of alpha particles compared with low-level exposure to gamma rays.

(b) The results of several epidemiological studies reported over the last two decades allow the direct estimation of cancer risks related to exposure to alpha-particle-emitting radionuclides. A critical analysis of these results can be used to evaluate the validity of the assumptions applied to protection against alpha emitters.

(c) This report provides a detailed review of results from recent epidemiological studies of cancer risk and occupational exposure to radioisotopes of plutonium (mainly ^{238}Pu, ^{239}Pu and ^{240}Pu) and uranium (mainly ^{234}U, ^{235}U and ^{238}U). It updates previous reviews published by international organisations, specifically the BEIR IV Report (NRC, 1988), the IARC monograph on internal emitters (IARC, 2012) and the UNSCEAR 2016 Report on the biological effects of uranium (UNSCEAR, 2017). The present report constitutes the first comprehensive review of health risks associated with plutonium exposure to be published in over 30 years.

(d) The report presents calculations of the lifetime excess risk of lung cancer mortality associated with example scenarios of plutonium inhalation, similar to that performed previously for radon and its decay products in *Publication 115* (ICRP, 2010a). It discusses the uncertainties associated with these results, and their potential impact for radiological protection.

2. Methodology used

(e) The report focuses essentially on epidemiological studies published since 2000 in which organ/tissue-specific dose estimates are based on individual monitoring of internal exposure to plutonium or uranium. Individual annual exposure data, long duration of health surveillance in the cohort and validation of the dosimetric models used for individual organ/tissue-specific dose assessment, were the major criteria considered for inclusion of a study in the analysis of lifetime risks. Consequently, results contributing to this analysis derive from a limited number of cohorts.

(f) For plutonium, several studies have been performed, in North America, Europe and Russia. One joint case-control study has been performed in Europe, but was limited by its size. The two main studies are the cohorts of workers employed at the nuclear installations at Mayak in the Russian Federation and at Sellafield in the United Kingdom. Assessments of intakes and organ/tissue-specific doses for Mayak workers arising from the inhalation of plutonium have been based primarily on the interpretation of measurements of urinary excretion, taking account of workers' occupational histories and the physicochemical forms of the inhaled plutonium aerosols. Results from autopsy data have also been used to determine model parameter values. There has been a progression of biokinetic and dosimetric models used for this purpose over the last 20 years, most recently applying the methodology of the Commission. The report

details the recent Mayak Worker Dosimetry Systems (MWDS-2008 and MWDS-2013) and the one developed for the joint analysis of Mayak and Sellafield plutonium workers as part of a European Union SOLO project.

(g) The assessment of uranium-specific doses for workers employed in the nuclear fuel cycle (processing, concentration, enrichment and reprocessing operations) is difficult, due to the relatively fast clearance of uranium from blood circulation, variability of exposure to uranium compounds and differences in the methods used to monitor internal exposure. The solubility of the uranium compounds to which workers are exposed is an especially important parameter in determining lung doses from bioassay data. Cohorts of uranium miners were not considered in this report, as they were extensively discussed in *Publication 115* (ICRP, 2010a) and the major lung cancer risk identified in these cohorts is due to radon and its decay products.

3. Review of epidemiological results

(h) The epidemiological evidence on risks associated with plutonium is less extensive than that for radon and its progeny. Indeed, the first epidemiological results from underground hard-rock miner studies were published at the end of the 1960s whereas most of the results related to plutonium were published after the 1990s. Furthermore, the number of studies providing results on plutonium risks from intakes of plutonium is more limited than for radon progeny. In addition, the assessment of doses due to plutonium exposure is more complicated, due to the chemical nature of plutonium compounds, and the retrospective reconstruction of plutonium doses from bioassay measurements.

(i) Lung cancer risks resulting from plutonium exposure have been quantified through extensive study of the Russian Mayak workers, which includes a wide range of exposure levels. Risks at lower levels of plutonium exposure can be complemented by analysing other cohorts in Europe and North America. One of the major risks related to plutonium exposure is lung cancer. Several successive analyses of the Mayak cohort, based on different dosimetry systems and periods of follow-up, have provided estimates of the dose-response relationship. Lung cancer risk estimates for Mayak workers are compatible with estimates obtained in two European studies published in 2017, but which have relatively wide confidence intervals. The impact of statistical power, uncertainty in dose estimates and co-factors, like tobacco smoking, that may influence cancer development are considered, together with alternative dosimetric approaches.

(j) Results from the Mayak cohort also suggest an association between plutonium exposure and risks of liver and bone cancers. There is no consistent evidence of a positive dose-response between leukaemia risk and plutonium exposure.

(k) Epidemiological studies of cancer risk associated with uranium exposure are primarily of cohorts of workers exposed to different chemical forms of uranium. Published studies are collated and evaluated, but most of them do not provide information that fulfils all the criteria mentioned above for the estimation of risks specific to uranium exposure. In recent years, several studies were published using improved organ/tissue-specific dose calculations, but they remain inconclusive because statistical power was limited and some of the information needed to reconstruct doses was not recorded in the past. It is therefore not possible at present to quantify cancer risks per organ/tissue-specific doses from uranium on the basis of the published studies.

(l) A few recently published studies have also considered possible health effects other than cancer, mainly circulatory diseases (Annex A). Some results are suggestive of an association between plutonium or uranium exposure and an increased risk of circulatory diseases,

especially results from the Mayak worker cohort. However, at present, these studies do not permit definitive conclusions on the existence of non-cancer diseases associated with internal exposure to plutonium or uranium.

4. Quantification of lung cancer lifetime risk associated with plutonium exposure

(m)It is now possible to estimate the lifetime excess risk of lung cancer following inhalation of plutonium directly from epidemiological studies of plutonium workers. Calculations have been performed for illustrative scenarios with a total plutonium intake of 1 Bq, assuming either an acute or a chronic inhalation of either soluble plutonium nitrate or insoluble plutonium oxide. Lung doses were calculated using models from *Publication 141* (OIR Part 4; ICRP, 2019). Lifetime risks were calculated using ICRP baseline rates for a Euro-American male population and the risk model from the SOLO project analysis of Gillies et al. (2017). These unitary intake scenarios should be considered only as examples, to provide an estimated order of magnitude of the risk and to illustrate variations in the dose and risk for the inhalation of plutonium.

(n) For the same intake, the cumulative doses to lung tissues from ^{239}Pu oxide are higher than those from ^{239}Pu nitrate, but the lifetime excess risk of lung cancer mortality per mGy varies little, with estimates between 1.4 and 1.7 per 10,000 persons, depending on the solubility (plutonium nitrate or plutonium oxide) and exposure rate (acute or chronic intake). In comparison, the lifetime baseline risk of lung cancer mortality is 631 per 10,000 persons for a Euro-American male population.

(o) For comparison, exposure to radon-222 progeny under the scenario considered in *Publication 115*, of 7.1 mJ h m^{-3} (2 WLM) per year from age 18 to 64 years, when converted to lung dose, leads to a lifetime excess risk of lung cancer mortality per mGy of 1.6 per 10,000 persons.

5. Implication for radiological protection and future research

(p) A comparison of the lifetime excess risk of lung cancer mortality from exposure to an external source of gamma radiation (based on the Life Span Study of the Japanese atomic-bomb survivors) and from internal exposure to plutonium (based on the Mayak workers study) indicates that, for the same absorbed dose to the lung and dose distribution, the risks from plutonium exposure are larger than those from external gamma exposure by a factor of about 16. The risk for radon progeny exposure appears consistent with that from plutonium exposure, larger than that from external gamma exposure by a factor of about 14, despite the very different distribution of alpha-particle dose within the lung.

(q) These comparisons suggest a biological effectiveness of alpha particles relative to high energy photons of about 14-16 for lung cancer. These values are compatible with the current radiation weighting factor (w_R) of 20 used by ICRP for alpha particles in the calculation of equivalent and effective doses (ICRP, 2007).

(r) It should be noted that this comparison is based on lung absorbed dose and lifetime excess risk of lung cancer mortality, with an application of a DDREF of 2 to the risk derived from the Japanese Life Span Study. Not applying a DDREF would lead to a relative biological effectiveness of about 7-8 for lung cancer. Also, care has to be taken in making comparisons with w_R as the latter is intended to embrace the risk of all stochastic effects whereas only lung cancer mortality is considered in the present calculations. Further, it was considered premature

to quantify lifetime excess risks for bone and liver cancers, for which associations have also been demonstrated for plutonium and different relative biological effectiveness values for alpha radiation may apply for these cancer types.

(s) Further research is needed to improve the assessment of health risks assocated with plutonium or uranium exposure, in epidemiology, dosimetry and risk modelling. Uncertainties associated with uranium and plutonium exposure and dose reconstruction are substantial, and inhalation of different chemical forms leads to very different cumulative organ/tissue-specific absorbed doses. Important efforts have been made in recent years to improve dose assessment and to consider the potential impact of uncertainties on risk estimates, and should be maintained in the future. Also, extension of existing cohorts and combined analyses of data are needed to increase power and allow a better estimation of the risks associated with plutonium and uranium exposures. For uranium, distinction of the different chemical forms of uranium componds in future analyses is higly desirable. Future research may better characterise the risks associated with alpha particles emitted by plutonium for cancer induction in organs other than lung.

1. INTRODUCTION

1.1. Cancer risk from exposure to alpha emitters

(1) Estimates of the excess risk of cancer following exposure to ionising radiation are largely derived from epidemiological studies of people acutely exposed to moderate and high doses of gamma rays, primarily the Life Span Study (LSS) of the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki in 1945. To obtain risks that would apply at low doses and low dose rates of exposure to low-linear energy transfer (low-LET) radiation (i.e. γ ray, x ray and β radiation), the Commission reduces the risk determined at moderate-to-high doses and high dose rates by a dose and dose rate effectiveness factor (DDREF).

(2) The system of radiological protection recommended by the Commission applies not only to such circumstances of exposure to low-LET radiation, but also to all other situations including intakes of alpha-particle-emitting radionuclides that deposit energy heterogeneously between and within organs/tissues of the body and continue to irradiate these organs/tissues with short-range alpha particles over a prolonged period, often many years. In addressing these exposure conditions using risk estimates derived from the LSS, a number of assumptions are made regarding the equivalence and additivity of external and internal exposures, the relative biological effectiveness (RBE) of alpha particles compared with gamma rays, and the effect of protracted exposure versus acute exposure.

(3) These assumptions can be tested using appropriate epidemiological studies of those exposed to internally deposited alpha emitters. There are good data obtained over several decades on lung cancer in underground hard-rock (e.g. uranium) miners who inhale radon-222 (^{222}Rn) and its radioactive decay products. Risks, doses, and protection against exposure to radon and its progeny have been considered by the the Commission in several publications (*Publications 115, 126 and 137* (ICRP, 2010a, 2014, 2017)).

(4) Over the past two decades or so, studies have been published of those exposed to radioisotopes of plutonium and uranium, radionuclides that distribute in the body, specifically in the lung, differently from radon and its progeny. In particular, radon and its decay products deliver doses primarily to the upper lung (bronchi) and briefly, whereas plutonium and uranium deliver doses throughout the lung and over a protracted period, especially so for plutonium. In this report these epidemiological studies of plutonium and uranium exposures will be reviewed and the implications of the findings for radiological protection discussed. This report provides a detailed review of results from epidemiological studies considering cancer risk from occupational exposure to plutonium and uranium published over the last 20 years. It aims to update previous reviews published by international organisations, especially the BEIR IV Report (NRC, 1988), the IARC monograph on internal emitters (IARC, 2012) and the UNSCEAR 2016 Report on the biological effects of uranium (UNSCEAR, 2017). The present publication constitutes the first comprehensive review of health risks associated with plutonium exposure.

(5) It focuses on recent epidemiological studies in which organ/tissue-specific dose estimates are used, based on individual monitoring of internal exposure to plutonium or uranium. The dosimetric methodology for the calculation of organ/tissue-specific doses from internally deposited plutonium and uranium is reviewed and discussed, and the importance of obtaining accurate doses for use in epidemiological studies is emphasised.

(6) Epidemiological studies of cancer risk associated with uranium exposure have been conducted among cohorts of European and North American workers exposed to different

chemical forms of uranium in the nuclear fuel cycle. These studies have been reviewed in the UNSCEAR 2016 Report (2017) and the present report updates the UNSCEAR review. Evidence from studies of uranium workers, however, remains limited.

(7) For plutonium, the two main studies are the cohorts of workers employed at the nuclear installations at Mayak in the Russian Federation and at Sellafield in the United Kingdom. Lung cancer risks resulting from plutonium inhalation have been quantified through an extensive study of the Mayak workers, which includes a wide range of exposure levels. Risks at lower levels of plutonium exposure are complemented by analysing other cohorts in Europe and North America, although the cohort of Sellafield plutonium workers remains of principal importance among these studies. Recent studies of the Sellafield workforce have provided estimates of the dose-response relationship for lung cancer that are comparable with those obtained in several successive analyses of the Mayak cohort, based on different dosimetry systems and periods of follow-up.

(8) Calculations of the lifetime excess risk of lung cancer mortality following inhalation of plutonium may be performed for unitary intake scenarios using dosimetric models from *Publication 141* (OIR Part 4; ICRP, 2019), baseline mortality rates for a Euro-American male population (ICRP, 2007) and the risk model from latest analysis of the Mayak cohort (Gillies et al., 2017). This provides an estimated order of magnitude of the risk and can illustrate variations in the lung dose and consequent risk for the inhalation of plutonium under different conditions of exposure. The results may be compared with the lifetime excess risk of lung cancer mortality per unit lung dose from inhalation of ^{222}Rn and its progeny, under the scenario considered in *Publication 115* (ICRP, 2010a), and with that following exposure to external gamma radiation, based on the experience of the Japanese atomic-bomb survivors. With respect to lung cancer, these comparisons provide information on the biological effectiveness of alpha particles emitted from plutonium and radon progeny relative to high-energy gamma radiation, which is relevant to the radiation weighting factor for alpha particles used for the purposes of radiological protection.

1.2. Exposure to plutonium

(9) Plutonium is an actinide element formed in nuclear reactors, mainly as the ^{238}Pu, ^{239}Pu, ^{240}Pu, ^{241}Pu, ^{242}Pu isotopes; and ^{239}Pu is the principal fissile material used for the production of nuclear weapons. ^{239}Pu, with a radioactive half-life of 24,065 years, was first produced artificially and identified in 1941 at Berkeley, USA. It exists naturally on Earth in minute quantities when ^{238}U nuclei absorb neutrons generated by the spontaneous fission of uranium isotopes, and was first separated by Seaborg and Perlman in 1949. ^{239}Pu is produced in nuclear reactors when ^{238}U captures a neutron, the ^{239}Np (half-life 2.356 days) so-formed undergoing beta-decay to ^{239}Pu. The longer uranium fuel is irradiated in a reactor the greater is the proportion of other isotopes of plutonium that are formed, as the plutonium isotopes capture neutrons. For example, when ^{239}Pu captures a neutron, ^{240}Pu is created ($t_{1/2}$=6561 years), and ^{238}Pu is formed from various neutron absorption reactions in uranium and neptunium isotopes. ^{238}Pu has a relatively short half-life of 87.7 years, and a correspondingly high specific activity and decay heat: 1 gram of ^{238}Pu generates about 0.5 watts of thermal power. Pure ^{238}Pu is produced by neutron irradiation of ^{237}Np, recovered from spent nuclear fuel. It produces little hazardous penetrating radiation, and so has found industrial applications in Radioisotope Thermoelectric Generators (RTGs), used for example in cardiac pacemakers and spacecraft, and Radioisotope Heater Units (RHU) used in spacecraft to heat critical components. ^{241}Pu is produced in higher ‘burn-up’ nuclear fuel as more neutron capture reactions occur, and decays

by beta-transformation (with a half-life of 14.35 years) to ^{241}Am, an alpha emitter with a half-life of 432 years. The longest-lived isotope of plutonium is ^{244}Pu with a half-life of 81 million years. Plutonium behaviour in the human body depends on its chemistry and is discussed in former publications (ICRP, 1972, 1986, 1993, 2019).

(10) Plutonium was first separated on an industrial scale from irradiated nuclear fuel in 1945 at the Hanford site in Washington State, USA. It was there that the plutonium was produced for the atomic bomb detonated over Nagasaki on 9 August 1945. Plutonium continued to be produced at Hanford to build up the nuclear weapons arsenal of the USA. Other sites reprocessing irradiated uranium fuel were also constructed and operated in the USA to produce weapons-grade plutonium (with a high ^{239}Pu content), such as the Savannah River and Rocky Flats sites.

(11) Efforts to produce plutonium in the former USSR started shortly after the end of the Second World War. The first Russian nuclear complex, currently known as the 'Mayak Production Association (PA)', was built for this purpose in the Southern Urals of Russia. This complex included nuclear reactors, a radiochemical plant, a plutonium production plant and a number of auxiliary facilities; the only facilities with potential for significant plutonium exposures were the radiochemical plant and the plutonium production plant. The first reactor was started in 1948 and the plutonium plant was built a year later. The first 10 years (1948-1958) of Mayak PA operations were the period of development of industrial-scale technology for producing plutonium.

(12) Exposures at the Mayak radiochemical plant involved substantial exposures to external radiation from short-lived fission products and to aerosols containing mostly plutonium nitrate, whereas exposures at the plutonium production plant involved intake of aerosols containing plutonium dioxide or mixtures of plutonium-containing salts combined with comparatively low doses of external radiation. The levels of exposure to plutonium were dependant on the workplace, period of employment, the work undertaken and whether workers used individual respirators that protected the airways. The highest exposures occurred during the period 1948-1958 before respirators were introduced. The highest exposures among workers employed during this period of time were among chemical engineers and chemical technicians employed in jobs related to enrichment of plutonium solutions, extraction of plutonium from these solutions and processing of plutonium in metal or dioxide form.

(13) Plutonium for the nuclear weapons programme of the UK was first produced at Windscale Works, Sellafield, in Northwest England, in 1952. Like the plutonium production sites in the USA and then in the USSR, Windscale Works consisted of nuclear reactors, a chemical reprocessing plant and a plutonium finishing plant. Exposures to plutonium at Sellafield in the early years of production were greater than in later years, but did not reach the levels experienced in the early years of operations at Mayak. Later, weapons-grade plutonium was also produced in France and China.

(14) In addition to nuclear weapons programmes, plutonium has also been separated from irradiated nuclear fuel in reprocessing plants for civil purposes, primarily for use as a fuel in nuclear power stations. Civil plutonium is usually derived from fuel with a higher 'burn-up' – the uranium fuel has been kept in a reactor for longer periods and has a higher content of plutonium isotopes other than ^{239}Pu, e.g. ^{240}Pu and ^{238}Pu. This change in the 'spectrum' of alpha-emitting radioisotopes and their chemical forms leads to potential exposure to aerosols with increased contributions from ^{238}Pu and ^{241}Am to the total alpha activity and smaller aerosol particle size due to particle fragmentation attributed to nuclear recoil during radioactive decay of ^{238}Pu.

1.3. Exposure to uranium

(15) Uranium is an actinide metal and is the most massive element (atomic number, 92) to be present in any quantity in the Earth's crust. Uranium has no stable isotope, but two isotopes are sufficiently long-lived for primordial uranium nuclei to be present on Earth today: ^{238}U has a half-life of 4.47×10^9 years while ^{235}U has a half-life of 7.04×10^8 years. ^{234}U also has a relatively long half-life of 2.46×10^5 years, but is only present on Earth because it is part of the radioactive decay chain of ^{238}U. The uranium presently found on Earth consists of 99.27% ^{238}U and 0.72% ^{235}U (and 0.01% ^{234}U as a result of the presence of ^{238}U); around half of the ^{238}U initially present on Earth has decayed by today, whereas only about 1% of the original ^{235}U now remains.

(16) Uranium is naturally present in varying concentrations in soil and rocks and in surface and ground water (UNSCEAR, 2000). A large portion of natural background radiation in the environment originates from radionuclides in the radioactive decay chains of ^{238}U and ^{235}U. With the isotopes in equilibrium, ^{238}U and ^{234}U each contribute approximately 48.9 % of the total activity content of natural uranium with ^{235}U contributing the remaining 2.2% (ATSDR, 2013). When the content of ^{235}U or ^{234}U is greater than that in natural uranium, the material is referred to as 'enriched' uranium, while uranium with a ^{235}U or ^{234}U content less than naturally occurring uranium is referred to as 'depleted' uranium. Enriched uranium is produced in specialist uranium enrichment plants for use in fuel for commercial nuclear reactors, typically at a ^{235}U enrichment of 3-5%, and at higher ^{235}U enrichments for use in research and military reactors, and in weapons. A by-product of the enrichment process is depleted uranium.

(17) Uranium exhibits both chemical and radiological effects. The chemical effects are independent of the isotopic make-up of the uranium compound. These effects are non-carcinogenic and assumed not to occur below a certain concentration. Uranium compounds vary greatly in solubility which can lead to differences in the bioavailability of the compound after inhalation or ingestion. Solubility of the compound varies according to valence, with the tetravalent form less soluble than the hexavalent form.

(18) In addition to the chemical toxicity of uranium, all uranium isotopes emit alpha particles on radioactive decay, which are classified as carcinogenic to humans by the International Agency for Research on Cancer (IARC, 2001, 2012). Although ^{238}U is the most abundant naturally occurring isotope, many other isotopes, ranging from ^{232}U to ^{237}U, continue to be handled to varying extents within the nuclear fuel cycle. Some of them, for instance ^{232}U (an alpha emitter with a half-life of 72 years), produce progeny that emit alpha particles, beta particles, and gamma rays.

(19) The potential for uranium exposure occurs throughout the nuclear fuel cycle: mining and milling of uranium; uranium conversion and enrichment; reactor fuel fabrication; reactor operation; nuclear fuel reprocessing; waste handling and disposal; and research and development. Inhalation is the principal means of intake of uranium in the uranium fuel cycle, and the chemical form of intake is important in determining the organ/tissue-specific doses received, in particular, by the lung, insoluble forms of uranium residing for a longer time in the lung and giving a higher cumulative dose.

1.4. Assessment of internal exposure to radionuclides

(20) Doses from intakes of radionuclides cannot be measured directly. Intakes are estimated from measurements of activity in the body or in excreta using biokinetic models.

Most alpha-particle-emitting radionuclides cannot be measured directly in vivo, unless the alpha decay is accompanied by a reasonably high energy gamma ray that can be detected outside the body, as in the case of ^{241}Am. They are therefore usually monitored by urine bioassay, and more rarely by faecal bioassay. Biokinetic models are constructed to provide a mathematical description of the uptake and retention of radionuclides in body organs and tissues and their excretion over time after intake by inhalation or ingestion (and occasionally, wounds). Such models are also used to determine the number of radioactive transformations occurring in different organs and tissues over specified time periods and absorbed doses are then calculated using dosimetric models (ICRP, 2015). Incorporated long-lived radionuclides such as isotopes of plutonium and uranium which can be tenaciously retained in the body may continue to irradiate tissue for many years after intake.

(21) Inhalation is a common route of occupational intake. A large uncertainty is usually associated with estimated internal doses following inhalation. The reliability of estimated intakes and doses depends notably on the quality of measurements, characteristics of the inhaled material, particularly its solubility and rate of absorption from lungs to blood, variations in individual physiological characteristics, and the time between exposure and measurement. Generally, these factors are not well known and estimates of internal doses are subject to substantial uncertainties.

(22) The most commonly used biokinetic and dosimetric models are those of the Commission as described in previous Publications. The Human Respiratory Tract Model (HRTM) of *Publication 66* (ICRP, 1994a), revised in *Publication 130* (ICRP, 2015), considers both the extra-thoracic and the thoracic airways and the interstitial tissues of the lungs. The thoracic airways (lung) is divided into three regions for which doses are calculated separately: the bronchial region (BB), the bronchiolar region (bb) and the alveolar-interstitial (AI) region. The fraction of inhaled activity that is deposited in those regions mainly depends on the particle size distribution of the inhaled aerosol, which is characterised by the activity median aerodynamic diameter (AMAD) and geometric standard deviation (GSD). The HRTM treats clearance as a competitive process between absorption into blood, which depends on the solubility of the inhaled material, and particle transport to the alimentary tract and lymph nodes. It is assumed that particle transport rates are the same for all materials, whereas absorption into blood is material specific. Different solubilities of chemical forms of uranium and plutonium lead to substantially different retention times in the lungs and hence magnitude and duration of dose delivery.

(23) In the HRTM, absorption is treated as a two-stage process: dissociation of the particles into a material that can be absorbed into blood (dissolution); and absorption into blood of soluble material and of material dissociated from particles (uptake). To represent time dependent dissolution, a fraction f_r of the deposited particles is assumed to dissolve rapidly at a rate s_r while the remaining fraction (1-f_r) is assumed to dissolve more slowly at a rate s_s. Dissolution depends upon the chemical form of the inhaled material whereas subsequent uptake to blood depends on the element. Uptake is usually assumed to be instantaneous unless the dissolved ions become bound to respiratory tract tissues. To represent time dependent uptake a fraction f_b of the dissolved material may be considered to be retained in a 'bound state', from which it is transferred into blood at a rate s_b and not subject to particle transport (ICRP, 1994a, 2015).

(24) The Human Alimentary Tract Model (HATM) of *Publication 100* (ICRP, 2006), replacing the former Gastro-Intestinal Tract Model (GITM) of *Publication 30* (ICRP, 1979), describes the intake of radionuclides by ingestion, their absorption to blood and excretion into

faeces. It also deals with activity transferred from the respiratory tract or from the systemic circulation, mostly through the liver. The absorption from alimentary tract to blood is quantified by the fraction f_A of ingested activity.

(25) The biokinetics of an inhaled radionuclide after absorption from the lungs to blood depends on the element. Direct information on the biokinetics of systemic uranium and plutonium comes from studies of human subjects injected with isotopes of the elements and autopsy data of exposed subjects. Studies of a variety of laboratory animals fill gaps in information for humans (ICRP, 2017, 2019).

(26) For adults, following uptake to blood, about 80% of plutonium is transferred to liver and skeleton, and the remaining is transferred to kidney and other soft tissues. A significant proportion of plutonium is tenaciously retained in the skeleton, while limited urinary and faecal excretion takes place. From the liver a small proportion of the activity is transferred to the alimentary tract via the bile and that remaining is recycled back to blood (ICRP, 1993, 2019).

(27) For adults, following uptake to blood approximately 75% of uranium is excreted in urine over the following few days and approximately 15% is deposited on bone surfaces. The remaining 10% of uranium is transferred to liver, red blood cells and other soft tissues, while limited faecal excretion takes place (ICRP, 1995, 2017). The biokinetics of uranium in the skeleton is similar to that of calcium but only a small proportion is retained over the long term because of bone remodelling and continuing urinary excretion.

(28) The skeleton is composed of compact cortical bone, including medullary cavities, and spongiosa, made of a lattice of thin trabecular bone and marrow (ICRP, 1996). Plutonium and uranium from the bloodstream deposit on bone surfaces, and then they may be buried in bone volume by formation of new bone or released from bone surface by resorption and returned to bone marrow and to blood (ICRP, 1989).

2. CANCER RISKS FROM EXPOSURE TO PLUTONIUM

2.1. Introduction

(29) Production of plutonium on a large scale requires several technological stages including:

- irradiation of uranium fuel in nuclear reactors,
- chemical dissolution of irradiated uranium fuel,
- chemical separation of plutonium from untransmuted uranium, transplutonium elements and fission products, and
- chemical extraction of plutonium from the resulting solution and its purification.

(30) These stages are usually subdivided into three specific components: nuclear reactors, radiochemical cycle and plutonium production cycle. Hence, exposure to plutonium occurs predominantly in occupational settings, and workers from radiochemical and plutonium production plants have the greatest potential for exposure to plutonium.

(31) Following inhalation and deposition in the respiratory tract, plutonium is cleared by particle transport to the alimentary tract and lymph nodes, and by absorption to blood. The rate of clearance to blood depends on the chemical form of the inhaled plutonium; for example, plutonium is absorbed to blood at a higher rate when inhaled as the nitrate than as the oxide. After absorption to blood, plutonium distributes in organs and tissues, primarily the liver and skeleton.

(32) Cancer risk resulting from plutonium exposure has been quantified through extensive studies of the Russian Mayak workers, who experienced a wide range of exposure levels. Estimates of risks at lower levels of plutonium exposure are complemented by analyses of other worker cohorts in Europe and North America, mainly the workers at Sellafield in the UK. One of the major risks related to plutonium inhalation is lung cancer, but plutonium also deposits on bone surfaces and in the liver, giving rise to risks of bone and liver cancers. The epidemiological studies of Mayak workers and other worker cohorts informing on cancer risk from plutonium are reviewed in this section and lifetime risks of lung cancer mortality are calculated.

2.2. Dosimetric aspects

(33) Assessments of internal dose have been carried out for plutonium workers at the Mayak PA, at Sellafield and at some other European and US sites. The methodologies and the assumptions made in these calculations are described below. The dosimetry performed for the main epidemiological studies of the Mayak workers cohort and the joint Sellafield and Mayak workers cohort are explained first, then that applied in other European and American studies is described. The most recent ICRP models (ICRP, 2015, 2017, 2019) are used for the most recent Mayak and Sellafield analyses; previous versions of the ICRP models have been used in earlier analyses; alternative modelling approaches have also been used to estimate lung dose and urinary excretion.

2.2.1. Mayak Worker Dosimetry System 2008

(34) Assessments of intakes and organ/tissue doses of the Mayak workers arising from the inhalation of ^{239}Pu have been primarily based on the interpretation of urine bioassay data. The

biokinetic and dosimetric models used for this purpose have been updated over the years (Khokhryakov et al., 2002, 2005). The Mayak Worker Dosimetry System 2008 (MWDS-2008) was developed as a collaborative effort between Russian, UK and US dosimetrists, which implements a modified version of the ICRP Human Respiratory Tract Model (ICRP, 1994a), the *Publication 30* GI tract model (ICRP, 1979) and the systemic biokinetic model for plutonium described by Leggett et al. (2005), which is consistent with the biokinetic model for plutonium of *Publication 141* (ICRP, 2019). The MWDS-2008 is described in detail by Khokhryakov et al. (2013) and the principal characteristics of this system are described below.

(35) The autopsy data of Mayak workers showed greater retention of insoluble forms of plutonium in the pulmonary tissues for smokers compared with non-smokers. Consequently, smokers and non-smokers were treated separately and the default HRTM particle transport rates were modified for smokers as described in *Publication 66* (ICRP, 1994a). When the smoking status was unknown, it was assumed that males were smokers and females were non-smokers. Aerosols of plutonium were divided into three categories according to their absorption characteristics, i.e. their chemical properties. These categories were:

- plutonium nitrates,
- plutonium oxides, and
- a mixture of plutonium compounds (nitrates, chlorides, oxalates, oxides and dioxides).

(36) Absorption parameter values were derived for each category by fitting model predictions to autopsy data. The autopsy data showed a higher than expected plutonium burden in the respiratory tract relative to that in systemic tissues at extended times after intake. To model this, the bound state of the HRTM was used to represent a fixed deposit of plutonium activity in the respiratory tract, which is not subject to particle transport or absorption (Khokhryakov et al., 2005). For non-smokers, values for the bound fraction were about 0.3 for oxides and 0.04 for nitrates. The assumed fixed deposit may actually represent particulate material deposited in the AI region that is sequestered in the interstitium or material that has become encapsulated in fibrous scar tissue.

(37) The autopsy data also showed that the ratio of plutonium in the pulmonary lymph nodes and in the lung parenchyma was higher than predicted by the HRTM. To reflect this, the particle transport rate from the AI region to the thoracic lymph nodes (LN_{TH}) was modified by fitting model predictions to the autopsy data (the ratio of the lymph node burden to systemic burden), (Khokhryakov et al. 2013).

(38) The intake regime for each worker was based on their exposure history with the exposure pattern assumed to be chronic but decreasing exponentially with time. The rate of decline was estimated for each type of workplace. However, if a worker had inadvertently been exposed to an acute intake because of an accident then they were excluded from the cohort. The size distribution of the inhaled aerosols was assumed to be lognormal with an AMAD of 5 μm and a GSD of 2.5, which are the ICRP default values for occupational exposures (ICRP, 1994a).

(39) Before the late 1970s many of the workers were given DTPA, (a chelating agent) prior to their urine sample to enhance their excretion. This improved the detection capabilities. It was estimated that on average the Ca-DTPA increased their urine excretion of plutonium by a factor of about 62. This factor was uniformly applied to estimate the 'natural' urinary excretion rate (i.e. the excretion rate if DTPA had not been administered). This enhancement factor is consistent with other values from 1 to 130 reported in the literature (Davesne et al., 2016), most being around 50, but it introduces an addition source of uncertainty in the estimate urinary

excretion rate that Vostrotin et al. (2017) quantified with a geometric standard deviation of 1.85.

(40) The intakes were estimated by fitting model predictions to the urinary excretion data by applying the maximum likelihood method (ISO, 2011). It was assumed that the uncertainty associated with the urinary excretion data could be described by a lognormal distribution with a given GSD. However, for simplicity, each data point was assumed to have the same GSD, in which case the estimated intake is independent of the GSD. If the measurement was below the decision threshold (DT) then the value was set equal to DT/2.

(41) The absorbed dose to the lung was calculated by dividing the energy deposited in the lung (excluding the lymph nodes) by the total mass of the lung. This is approximately equal to the absorbed dose to the AI region and it assumes that the sensitivity per unit mass of the central airways (BB and bb regions of the lungs) is the same as that of the AI region. The energy deposited due to alpha recoil was excluded in the calculation. If the body mass was known, the estimated absorbed dose to lung (and to other organs) was adjusted by multiplying the dose by the ratio of body mass for the reference worker to the actual body mass. This may have introduced some biases in lung doses as the masses of the radiosensitive regions of the lung are not necesserilly proportional to the body mass. When the individual body mass was unknown, an assumption was made that the lung mass was 1.1 kg for a male worker and 0.904 kg for a female worker.

(42) The MWDS-2008 analysis assumes that all the alpha-activity arises from ^{239}Pu. The exact radionuclide composition of the inhaled material was not considered. However, other nuclides such as ^{238}Pu, ^{241}Pu and ^{241}Am would also be present in the source term and furthermore the activity composition would change with time. *In-vivo* measurements with a whole-body counter showed that the fraction of ^{241}Am in the total body relative to the sum of actinides was sometimes as high as 15% (Khokhryakov and Yefimov, 2007). Taking account of the radionuclide composition of the source term will affect the individual's dose assessment and neglecting it is an additional source of uncertainty.

(43) Although about a third of workers employed in plutonium production or radiochemistry in the early 1950s were monitored for plutonium by urinalysis (Shilnikova et al., 2003), a systematic urine monitoring program did not begin until about 1970. As a result, only about 40% of the workers in the radiochemical and plutonium plants had internal dose assessments based on urine monitoring. Of these 40%, only about a third had more than two urine measurements. However, for the workers with lung absorbed doses exceeding 0.2 Gy, approximately half had more than two urine measurements. For approximately 73% of workers, their first plutonium measurement in urine was taken during the second half of their career.

2.2.2. Mayak Worker Dosimetry System 2013

(44) Mayak Worker Dosimetry System was further developed in 2013 by the same international group. The revised Mayak Worker Dosimetry System (MWDS-2013) used to assess doses to the lungs and other organs/tissues of the plutonium workers at the Mayak Production Association was based on the revised HRTM that was later adopted in *Publication 130* (ICRP, 2015). New absorption parameter values for plutonium oxides and nitrates have also been derived. As with the MWDS-2008, the *Publication 30* GI tract model (ICRP, 1979) and the systemic biokinetic model for plutonium described by Leggett et al. (2005) were implemented. In addition, uncertainties associated with dose estimates were calculated taking account of uncertainties in both the urine measurement data and the model parameters. In a Bayesian approach, the uncertain quantities are represented as random variables following

probability distributions. Prior distributions are first assigned based on initial knowledge. Then the prior distributions are updated to incorporate information from measurement data. The updated probability distributions are called posterior distributions, and the updating is accomplished by applying Bayes' Theorem, an elementary result of probability theory (NCRP, 2010). Bayesian techniques were applied in MWDS-2013 to calculate posterior distributions on doses derived from urinary data. A description of the dosimetry system is given by Birchall et al. (2017a). The main differences between this system (MWDS-2013) and the previous system (MWDS-2008) are described below.

Respiratory tract model parameter values

(45) Prior distributions were assigned to respiratory model parameter values including aerosol size parameters, breathing parameters, deposition efficiency parameters, particle transport parameters and absorption parameters (Birchall at al., 2017a). Most of the prior distributions were derived and justified by Puncher et al. (2011) for a European workers study (Tirmarche et al., 2010). However, notable exceptions are the absorption parameters associated with the assumed bound state (f_b and s_b), and the slow dissolution rate s_s for plutonium nitrates and oxides.

(46) The revised HRTM of *Publication 130* has adopted a new particle clearance model for the AI region which models observations of greater retention in the AI region than assumed previously for insoluble particles. Approximately 33% of the alveolar deposit of insoluble particles is assumed to be sequestered in the interstitium, and as such not subject to particle transport other than very slow clearance to lymph nodes. Sequestration to the interstitium of relatively insoluble forms of plutonium is consistent with observed long-term retention in the lungs of Mayak workers.

(47) Circumstantial evidence of a bound state for plutonium comes from a reanalysis of historic beagle dog data where dogs were exposure to plutonium nitrate and followed for 15 years (Puncher et al., 2017b); and of autopsy and bioassay data of United States Trans-Uranium and Uranium Registries (USTUR) whole-body donor (Case 0269), a plutonium worker who inhaled plutonium nitrate (Puncher et al., 2017a; Tolmachev et al., 2017). In both cases, the absence of clearance by either uptake to blood or mucociliary clearance of the observed late retention was consistent with the definition of a bound fraction (ICRP, 2019).

(48) Autopsy data from 20 Mayak workers, exposed to nitrates only, were analysed to determine values of f_b and s_s (Puncher et al., 2017c). Using a Bayesian approach with the revised *Publication 130* HRTM, the mean value of f_b was determined as 0.0014. There was no evidence for a s_b value other than zero. The medium value determined for s_s for plutonium nitrate was 2.5×10^{-4} d^{-1}. Puncher et al. (2017d) also carried out a similar analysis on autopsy data from 20 Mayak workers, exposed to oxides only. The medium value determined for s_s for plutonium oxides was 4.7×10^{-5} d^{-1}.

Dosimetry assumptions

(49) Radiosensitive cells in each of the three regions of the lung have been identified for the purposes of the HRTM (ICRP, 1994a). These are basal (BB_{bas}) and secretory (BB_{sec}) cells in the bronchial epithelium; Clara cells (a type of secretory cell) in the bronchiolar epithelium; and endothelial cells such as those of capillary walls and type II epithelial cells in the AI region. The radiosensitive targets of the BB and bb regions are assumed to be restricted to tissue layers of given depths and thicknesses whereas in the AI region it is assumed the sensitive cells are

distributed homogenously throughout its mass. In the MWDS-2013, the absorbed dose to each target region was calculated:

- bronchial basal cells, D_{bas},
- bronchial secretory cells, D_{sec},
- bronchiolar region D_{bb}, and
- alveolar region, D_{AI}

(50) Where a single quantity is required to represent lung dose a 'detriment-weighted absorbed dose' to the lung was calculated in MWDS-2013 with the weighting scheme of the HRTM (ICRP, 1994a, 2015):

$$\text{Lung dose (Gy)} = 1/3 \times ([0.5 \times (D_{bas} + D_{sec})] + D_{bb} + D_{AI})$$

Owing to the much smaller mass of the target regions in the BB and bb regions than in AI, this apportionment assumes a substantially greater sensitivity per unit mass of the central airways than the lung tissue represented as AI. Calculating a 'detriment-weighted absorbed dose' as opposed to a mass-weighted absorbed dose, as was done in MWDS-2008, is preferable because the evidence on risks from radon progeny shows that the dose to central airways can result in lung cancer. Calculating lung dose as a mass-weighted absorbed dosewould result in the prediction of a lung cancer incidence in miner study groups exposed to radon that is lower than observed. Equal apportionnement of the detriment for the three regions of the lung provides much better consistency with the observed incidence (Marsh et al., 2014; Birchall and Marsh, 2017).

(51) No correction factor was applied to the lung dose to account for the variation in the mass of the lung between subjects (Birchall and Sokolova, 2017). However, separate doses to males and females were calculated with the ICRP reference organ masses for males and females (ICRP, 2002).

(52) In the revised HRTM of *Publication 130*, there are no modifying factors for particle transport rates for smokers because long-term lung retention studies of insoluble particles show no clear difference between smokers and non-smokers (Gregoratto et al., 2010). The dose calculations for the MWDS-2013 did not distinguish between smokers and non-smokers.

Urine measurement assumptions

(53) Workers stayed at an in-patient hospital for 72 hours in order to provide three consecutive 24-h urine samples. The urine measurements were used to provide an estimate of workers' average excretion rate over a 24-h period. If incomplete samples were collected, they were normalised to an equivalent 24-h value by considering either the volume of the sample or the amount of creatinine in the sample. Before 2008, urine samples were normalised by volume if the volume collected was small (< 0.5 L), while after 2008, all urine samples were normalised by creatinine concentration measurements. As explained above for the MWDS-2008 [*para.* (39)], for those workers who were given DTPA prior to their urine sample, a correction was made to account for the enhanced excretion due to the DTPA.

(54) The uncertainties associated with the urine measurements were estimated by Vostrotin et al. (2017). The uncertainties were expressed as a geometric standard deviation. These uncertainties included (1) measurement uncertainties due to counting statistics, (2) uncertainties associated with the collection period, and (3) variability in the enhancement factor for those workers given DTPA. These uncertainties were also applied to the urine data below the decision threshold (DT) but the contributions due to counting statistics were ignored.

Likelihood functions were derived for urine data above and below the DT, which can be used in a Bayesian analysis. About half of the urine measurements were below the DT.

Exposure assumptions

(55) Based on personal or static air sampling data, three separate time periods were identified during which average air concentrations were expected to be different (Sokolova et al., 2017). These were before 1958, 1958-1970 and after 1970 with median values of annual volumetric activity of alpha-emitting radionuclides in workplace air assumed to be 3.2, 0.32 and 6.4×10^{-3} Bq m^{-3}, respectively. The exposure pattern was therefore simplified to a stepwise function corresponding to three levels of constant chronic intake with relative concentrations of 1:0.1:0.002. A relatively uninformative prior was assigned to the total intake described by a lognormal distribution with a GSD of 6 (Birchall et al., 2017a). The medium value, *M*, of this prior was assumed to be proportional to the number of years of exposure. It was shown that the dose estimates were not overly sensitive to the value of M (Puncher et al., 2014).

(56) Where there was direct evidence of additional acute intakes, the worker was excluded from the cohort.

2.2.3. Dosimetry for the joint cohort of plutonium workers from the Russian Federation and the United Kingdom

(57) A joint epidemiological analysis of Russian and British plutonium worker cohorts was undertaken to investigate potential associations between lung cancer and leukaemia mortality and incidence, and cardiovascular disease mortality, and occupational exposures to plutonium (Gillies et al., 2017). The study combined the Mayak Worker Cohort (MWC) and the Sellafield Worker Cohort (SWC). The dosimetry system used was similar to the MWDS-2013, which implemented the revised HRTM that was later adopted in *Publication 130* (ICRP, 2015), the *Publication 30* GI tract model (ICRP, 1979) and the systemic biokinetic model for plutonium described by Leggett et al. (2005). A Bayesian approach was adopted where uncertainties on model parameter values and intakes were first derived as prior probability distributions. However, absorbed tissue doses for the Mayak and Sellafield workers were provided as point estimates (i.e. single estimates without uncertainties). These point estimates were calculated for each worker based on their urinalysis data as follows (Puncher and Riddell, 2016): a Bayesian posterior distribution of intake was calculated using an assumed prior distribution on intake with the model parameter values fixed at their prior means. The best estimate of intake was taken as the mean of the posterior distribution which was then used to calculate absorbed doses to lung and other tissues/organs. This approach is also applicable to cases where all the urinalysis data are censored below the detection limit (DL) and leads to unbiased estimates of doses. This is important because 45% of the monitored workers in the pooled cohort had only urine measurements that were below the DL. Puncher and Riddell (2016) showed that the point estimates of dose produced for the epidemiological study are unbiased.

(58) A relatively uninformative prior distribution was assigned to the total intake described by a lognormal distribution with a GSD of 6. For the Sellafield workers, a constant chronic exposure over the exposure history was assumed, with additional acute intakes if direct evidence was available. The median value of the total intake prior was calculated for each Sellafield worker assuming 20 Bq per year and 20 Bq per acute intake. These values were derived from analysis of historical personal air sampler data (Puncher et al., 2014). The exposure pattern assumed for the Mayak workers was a stepwise function consisting of three

separated constant chronic intakes regimes as described above for the MWDS-2013 [*para.* (55)].

(59) The prior distributions assumed for the model parameters were the same as those for MWDS-2013 apart from the slow dissolution rate, s_s for plutonium nitrate (Puncher and Riddell, 2016; Birchall et al., 2017a). Different studies of humans inhaling plutonium nitrates suggested significantly different solubility in terms of the level of slow dissolution. For example, the lung, urine and systemic data from two volunteers who inhaled $^{237}Pu/^{244}Pu$ nitrate (Etherington et al., 2003) were re-analysed and a s_s value of 2.2×10^{-3} d^{-1} was estimated using a Bayesian analysis (Bull and Puncher, 2019). This value is significantly higher than the value assumed for the MWDS-2013 ($s_s = 2.5 \times 10^{-4}$ d^{-1}), which was based on autopsy data of 20 Mayak workers exposed to plutonium nitrates only (Puncher et al., 2017c). It was noted that the value derived from the volunteer experiment ($s_s = 2.2 \times 10^{-3}$ d^{-1}) was similar to that derived from rat studies of Sellafield plutonium bearing materials (Moody et al., 1993). As there was no consensus on which value to use, for the purposes of dose reconstruction, two sets of dose estimates were produced: one set based on a normal prior distribution for s_s with a mean of 2.2×10^{-3} d^{-1} (referred to as the 'Sellafield prior') and the other based on the 'Mayak prior' of MWDS-2013 for plutonium nitrates. Thus, the Mayak prior for plutonium nitrate assumes lower solubility than the corresponding Sellafield prior.

(60) On average the lung doses calculated for each worker of the SWC using the 'Mayak prior' are around 3 times higher than using the 'Sellafield prior' with a variation characterised by a geometric standard deviation of 1.4. As expected, there is little or no effect on systemic doses (liver and red bone marrow), and a small effect for intake.

(61) It was not clear whether the observed difference in long-term dissolution was due to differences in chemical processes (e.g. causing partial oxidisation of the nitrate material) at Mayak and Sellafield, different levels of exposure or to a difference in interpretation between an experimental study and autopsy results. Recently ICRP (2019) has reviewed human and animal studies following inhalation of plutonium nitrate to derive specific absorption parameter values (*Publication 141* - OIR Part 4). A s_s value of 2.0×10^{-3} d^{-1} is recommended based on:

- long-term monkey and dog studies with follow-up periods of 8 y and 15 y respectively (Brooks et al., 1992; Dagle et al., 1993; Pellow et al., 2019; Puncher et al., 2017b),
- analysis of autopsy and bioassay data of United States Trans-Uranium and Uranium Registries (USTUR) Case 0269, a plutonium worker who inhaled plutonium nitrate (James et al., 2007; Tolmachev et al., 2017; Puncher et al., 2017a), and
- the volunteer experiment discussed above (Puncher el al., 2016b).

(62) It was noted that a large fraction dissolving at a slow rate ($s_s = 2.5 \times 10^{-4}$ d^{-1}), as reported for Mayak workers based on autopsy data, was inconsistent with the results of the USTUR and the long-term dog and monkey studies, but it was considered that a slow rate could apply to higher levels of exposures (ICRP, 2019). The data available suggest that the different time scales of the volunteer study (~4 months) and the Mayak autopsy data (> 5 y) cannot explain the discrepancy in the assessed s_s values for the Sellafield and Mayak worker cohorts. The discrepancy likely reflects different exposure conditions in the two cohorts, in terms of industrial chemical processes, with the possible presence of residual insoluble material in some plutonium nitrate, and involved masses, with higher mass of plutonium nitrate inducing greater polymerisation of hydrolysed plutonium in the lung (ICRP, 1986; Nolibé et al., 1989).

(63) Urine sampling procedures at the Sellafield site changed after 1970 because of the discovery of a problem involving the adventitious contamination of urine samples arising from the re-use of glass sample bottles. By 1971 disposable plastic bottles were introduced. To take

account of this, pre-1971 urine data were divided by 3 and were assigned a larger measurement uncertainty (GSD= 2.8) compared with post-1970 data (GSD=1.6) (Riddell et al., 2000; Puncher and Riddell, 2016) (see section 2.2.5). Workers who only had pre-1963 urine results that were all recorded as 'less than the reporting level' were excluded from the SWC.

(64) For the Sellafield workers, the dose arising from intakes of ^{241}Pu was included in the dose calculation [*para. (77)*]. This was inferred from the expected activity ratio of ^{241}Pu to plutonium alpha emitters in the plant material on an annual basis. In comparison, the dosimetry for the Mayak workers assumed all the alpha activity arises from ^{239}Pu and did not take account of intakes of ^{241}Pu or ^{241}Am [*para. (42)*].

2.2.4. Dosimetry systems for other worker studies

2.2.4.1. European combined analysis of Plutonium Workers (Alpha-Risk European project)

(65) Grellier et al. (2017) investigated the effects of internal exposure to uranium and plutonium for workers in the British (AWE, UKAEA and BNFL cohorts), Belgian (SCK•CEN/BN cohort) and French (CEA-COGEMA cohort) nuclear industry in a case-control study of lung cancer and leukaemia mortality, nested within appropriate cohorts from the study by Cardis et al. (2007). The nested case-control design allowed detailed dose reconstruction as well as the collection of individual data on potential confounders. Bingham et al. (2017) describe the dosimetry in detail, which is summarised below.

(66) The systemic biokinetic model for plutonium described by Leggett et al. (2005) together with the *Publication 66* HRTM (ICRP, 1994a), were used to generate point estimates of lung dose. Transport through the gastrointestinal tract was based on the *Publication 30* model (ICRP, 1979). Doses were calculated using *Publication 23* (ICRP, 1975) reference organ/tissue masses and radionuclide transformation data from *Publication 38* (ICRP, 1983).

(67) Bioassay data obtained for controls after the date of cancer diagnosis of the matched case were excluded. This ensured that the dose assessments for controls were not biased by the availability of more accurate bioassay results compared to the cases. A maximum likelihood method was applied to provide an estimate of the intake(s) based on the best fit between the observed bioassay data and that predicted from the estimated intake regimes. At AWE, subjects with measurements that were all below the reporting level were excluded from the study. For UKAEA and CEA-COGEMA, a Bayesian fitting was used to provide a central estimate of the intake for such workers by extracting the median from the posterior probability distribution. For BNFL, the approach taken was that the last measurement result in the exposure period was set as positive at the limit of detection and chronic intake was assumed over the period.

(68) The individual alpha-particle doses to the bronchial, bronchiolar, alveolar-interstitial lung regions, thoracic lymph nodes and red bone marrow were estimated. For the main epidemiological analysis, the dose to the lung was calculated as the arithmetic mean of the doses to the bronchial, bronchiolar and alveolar-interstitial regions. The alpha-radiation dose from ^{241}Am in-growing from ^{241}Pu in the exposure material was included in the plutonium dose for the UKAEA, BNFL, CEA-COGEMA and SCK•CEN/BN cohorts.

(69) Dose assessment was essentially based on urine measurements, with variable numbers per subject. A small number of faecal and lung monitoring (at CEA-COGEMA) results was also used.

(70) Chronic intakes were assumed for any period of a worker's career that involved a potential risk of internal exposure by plutonium. The start and end dates of chronic intakes were determined from records of work history for the UKAEA and AWE cohorts and from

exposure files for the CEA-COGEMA cohort. Where these data were not available or did not align with the monitoring data, start and end dates were adjusted based on monitoring intervals and known periods of employment. By default, for BNFL workers, chronic exposure periods were started 6 months prior to the first sample for plutonium bioassay, as this was the usual monitoring interval. Evidence for acute intakes came from reports of incidents, from air-sampling data, from nose-blow results and from post-incident monitoring.

(71) An aerosol particle size of 5 μm AMAD was chosen as the most typical of workplaces. The lung solubility of the exposure material was based on information available on the materials used or known to be present in the workplaces (buildings) in which individuals had worked. The lung solubility parameter values used were derived by assigning the material to the appropriate HRTM default absorption type (ICRP, 1994b) or from experimental evidence or by re-evaluating historical intake assessments to obtain specific HRTM absorption parameters.

2.2.4.2. Sellafield workers

(72) Cohort studies of the plutonium workers employed at the Sellafield plant in NW England have been reported by Omar et al. (1999) and McGeoghegan et al. (2003). For these studies, annual doses to tissues/organs of individual workers arising from the inhalation of plutonium were calculated based on measurements of plutonium in urine. These older studies made use of older versions of the biokinetic models of the Commission and alternative modelling approaches have also been used to estimate lung dose and urinary excretion. Details of the calculations are given by Riddell et al. (2000) and are briefly discussed here.

(73) For the majority of the assessments a single constant chronic exposure was assumed. Assessments of systemic uptake of plutonium (i.e. activity transferred to blood) were obtained from the urine measurements by applying the Jones urinary excretion function (Jones, 1985). From the assessed uptake rate, the dose to the lungs, GI tract and systemic organs were calculated by implementing the ICRP biokinetic and dosimetric models available at the time of calculation. For the analysis carried out by Omar et al. (1999), these were the respiratory tract model and the GI tract model described in *Publication 30* (ICRP, 1979) and the systemic biokinetic model for plutonium described in *Publication 48* (ICRP, 1986).

(74) The *Publication 30* respiratory tract model classified material according to its solubility in terms of retention times in lung. The results presented by Omar et al. (1999) were for class Y, retained for years, materials only as measurements made on the solubility of plutonium compounds commonly found at Sellafield showed that the majority exhibit behaviour closest to Class Y. Compared with the current HRTM (ICRP, 2015) applied to the pooled cohort of Mayak and Sellafield workers (section 2.2.3), Class Y roughly translates to Type S, including plutonium oxide.

(75) The organ dose calculations carried out for the cohort study of female plutonium workers at the Sellafield plant (McGeoghegan et al., 2003) used updated biokinetic and dosimetric models, namely the *Publication 66* HRTM (ICRP, 1994a) and the *Publication 67* biokinetic model for plutonium (ICRP, 1993). However, a separate urinary excretion function (Jones, 1985) was still applied to assess the uptake of plutonium as the function was derived using Sellafield worker data.

(76) The uptake rate assessed from urine data with the Jones urinary excretion function was higher than expected when compared with uptake estimates obtained from autopsy data. Consequently, the calculated organ doses were reduced by a factor of 3 as it was judged that the autopsy data would provide a more accurate estimate of the true uptake (Riddell et al.,

2000). They were reduced by an overall factor of 9 when based on pre-1971 urine data due to substantial adventitious contamination of urine samples mentioned in *para* 63. Since the actual bias introduced by both the use of the Jones function and the contaminated pre-1971 glass sample bottles was not accurately quantified, it led to large uncertainty in historical Sellafield dose assessment. For workers where both pre-1971 and post-1970 urine data were available, only the post-1970 data were used in the assessment.

(77) In addition to the doses from 'Pu alpha' (i.e. from ^{239}Pu, ^{238}Pu and ^{240}Pu), the dose from ^{241}Pu intake and from its decay product, ^{241}Am, was also estimated. The ^{241}Pu intake was inferred from the expected activity ratio of ^{241}Pu to 'Pu alpha' of the plant material. The expected activity ratio changed annually to reflect changes in the prevailing plant conditions and the average recorded burn-up of the fuel reprocessed in each year (Riddell et al., 2000).

2.2.4.3. US nuclear workers

(78) The potential health hazards of internal exposure to plutonium were recognised in the United States since the early 1940's because it was an alpha emitter like radium, to which New Jersey dial painters were previously exposed (Rowland, 1994). As a consequence a Health Group was established in the Manhattan Project to implement occupational radiation safety that prevented workers from receiving significant plutonium intakes. Notably, in 1944, Wright Langham instituted a program for the collection of daily urine samples from Los Alamos National Laboratory employees handling plutonium. The Pu content of those samples was extracted with an iron carrier by cupferron in chloroform and measured with gas-flow proportional counters and a background of approximately 30 counts per minute. From 1945, urine samples were collected on vacation away from Los Alamos to avoid cross contamination and the measurement background was decreased to about 0.1 count per minute (Campbell et al., 1972; Miller et al., 2008).

(79) Then, the dosimetric interpretation of the Pu bioassay results was made possible by data collected in experimental studies (ICRP, 2019). For instance, biomedical studies began in 1944 with studies on rodents that indicated translocation of Pu from blood to liver and skeleton, with a long retention half-life in skeleton (Durbin, 1975, 2011). Moreover, from 1945 to 1948, 18 seriously ill persons were injected with tracer amounts of Pu citrate or nitrate to investigate the relation of the systemic burden and excretion rate of Pu (Langham et al., 1950; Langham, 1959). The life expectancies of the subjects were judged to be short at the time of injection, but eight were still alive after 8 years and four survived at least 3 decades (Rowland and Durbin, 1976). Thus, both the results of the human injections and the Los Alamos workers data were used by Langhman et al. (1950) to determine urinary and faecal excretion curves for Pu.

(80) In practice, about 6000 urine analyses were conducted on Los Alamos workers between 1944 and 1950. Twenty seven of the workers excreted measurable amounts of Pu. Their health was followed first by Langham and Hempelmann (Langham et al., 1962; Hempelmann et al., 1973) and later by George Voelz (Voelz et al., 1979, 1997). More recently, Miller et al. (2008) estimated their doses and those of an expanded group of 210 former Los Alamos workers from the years 1944–1945: the median effective dose was 75 mSv with a geometric standard deviation of 1.62.

(81) Schubauer-Berigan et al. (2007) carried out a nested case-control study of leukaemia excluding chronic lymphocytic leukaemia (non-CLL leukaemia) among workers at five US nuclear facilities. Both external and internal exposures were considered. Equivalent doses to the red bone marrow arising from exposures to plutonium were calculated from urine measurements by implementing ICRP biokinetic and dosimetric models (Daniels et al., 2006).

These included the *Publication 66* HRTM (ICRP, 1994a), the *Publication 30* GI tract model (ICRP, 1979) and the *Publication 67* biokinetic model for plutonium (ICRP, 1993). Evaluations were carried out only for those workers who had detectable plutonium in urinary excretion ($\geq$1.7 mBq d^{-1}). Occupational, dosimetry, medical and site records were reviewed to obtain information regarding date and route of exposure, isotopic composition of source term and plutonium solubility. Unless information was available to suggest otherwise, the following assumptions were made:

- Route of intake was inhalation.
- Intakes occurred 3 days prior to the first 'positive' bioassay sample.
- Solubility of material was 50% Type M (moderately soluble) and 50% Type S (slow absorption).
- Source term consisted of ^{239}Pu only.

(82) Lung doses arising from inhalation of plutonium and uranium have also been calculated for a case-control of workers employed at the Rocky Flats Plant in Colorado (Brown et al., 2004). These assessments were based on urine measurements of plutonium and uranium, and on lung *in-vivo* measurements. Intakes of ^{241}Am were inferred from the assessed ^{239}Pu intakes and the isotopic ratios of the nuclear materials processed at Rocky Flats. The biokinetic and dosimetric models described in *Publication 30* were used in the calculations (ICRP, 1979). For cases and controls, 98% and 96% of the collective internal lung dose, respectively, was due to a combination of plutonium and ^{241}Am.

(83) An earlier cohort study of Rocky Flats workers (Wilkinson et al., 1987) had used cumulative systemic plutonium depositions as calculated from urinalysis results, but tissue-specific doses were not estimated.

(84) A cohort study of Los Alamos workers (Wiggs et al., 1994) used cumulative systemic plutonium depositions based on urinalysis results and did not estimate tissue-specific doses. However, for a subset of 26 Manhattan Project workers (Voelz et al., 1997) annual tissue-specific doses were calculated using the models of *Publication 30* (ICRP, 1979).

(85) A cohort study of Hanford workers (Wing et al., 2004) did not use available bioassay results for plutonium, but preferred to use exposures derived from a job-exposure matrix.

2.2.5. Uncertainties in plutonium dose estimates

(86) The uncertainty in an internal dose assessment based on bioassay data, such as urinary measurements, arises from many sources of uncertainty:

- the uncertainty in the bioassay measurements,
- the uncertainty in the route of intake, the time and pattern of intake,
- the uncertainty associated with the chemical and physical form of the deposited radionuclide(s) such as the activity size distribution and the absorption characteristics of the inhaled material,
- the uncertainties in the identity of radionuclides and their relative abundances in the source term, and
- the uncertainties in the biokinetic and dosimetric models used to interpret the bioassay measurements.

(87) The US National Council on Radiation Protection & Measurements (NCRP, 2010) extensively reviewed these uncertainties and the methods used to evaluate them. In MWDS-2013, a multiple realisation approach was applied to assess uncertainty on dose in a Bayasian inference framework (Birchall et al., 2017c). The uncertainties in internal dose assessments

based on bioassay data can be quite large. This is illustrated by the work of Puncher and Riddell (2016). Using Bayesian inference techniques, they calculated posterior distributions of absorbed doses to lung for plutonium workers of the Sellafield plant (United Kingdom) based on urinary measurements. The analysis took account of the uncertainties in the biokinetic models, measurements of urinary excretion and estimates of intakes. The parameter values for each worker were assumed to be independent. The geometric mean values of the ratio of the 97.5%:2.5% posterior values were a factor of 100 for lung dose, and 30 for doses to liver and red bone marrow. It was inferred that the most important sources of uncertainty in lung dose were the uncertainties in the rapid absorption parameters (f_r, s_r) and the uncertainty in the pre-1970 urine measurement data [*para*. (63)].

(88) While Bayesian inference techniques have been used to calculate posterior distributions on internal plutonium doses based on urine data for epidemiological studies of plutonium workers from the Mayak and Sellafield plants (Puncher and Birchall, 2008; Tirmarche et al., 2010; Puncher and Riddell, 2016; Brichall et al., 2017c; Birchall and Puncher, 2017), further research is required to determine the appropriate methods of analysis of these data. Such an analysis will need to take account of shared and unshared errors. Shared errors are uncertainties that are 100% correlated between different workers whereas unshared errors assume no correlation between workers. Statistical techniques to estimate uncertainty in risk that reflects statistical sampling error and uncertainty in dose including shared errors have been described by Stayner et al. (2007). Generally, the error associated with internal doses can be considered as Berkson type because of the inability of the biokinetic and dosimetric model to predict the individual's true dose for a given exposure. It is noteworthy that the mean value of the posterior distribution of dose is generally greater than the point estimate of dose calculated with the best-estimate values of the input model parameters. This difference arises because the biokinetic and dosimetric models are non-linear with respect to most of their parameters.

(89) Typically, non-incident-specific intakes (i.e. background intakes) of actinides are modelled by assuming a constant chronic intake. However, truly chronic intakes are rare and plutonium workers may be exposed to a series of acute intakes. The uncertainty in the estimated intake associated with assuming a constant chronic intake was investigated by Wilson and Bull (2007). Artificial ^{239}Pu urinary datasets were created consisting of 4 urine samples per year over a ten-year period arising from two random acute intakes per year. Assuming a constant chronic intake over a ten-year period, resulted in an average systematic uncertainty in the estimated intake of about 4%. In comparison, the authors noted that the uncertainty associated with the solubility characteristics of the inhaled material can be a major source of uncertainty in dose assessment that are based on excretion data.

(90) The uncertainty in biokinetic models used to interpret bioassay measurements not only arises from uncertainties associated with model parameter values but also on the uncertainty associated with the structure of the model. Such uncertainties may arise because the structure of the model provides an over simplification of the known processes, because the model cannot account for unknown processes or because part of the model structure is based on mathematical convenience rather than the actual processes. For example, a volunteer study suggested that the early urinary excretion rate following inhalation of plutonium nitrate might be enhanced compared with that following intravenous injection (Etherington et al., 2003). The uncertainty in the biokinetic approach used may result in biased estimates of intakes and doses based on bioassay data. For instance, the evaluation of data for UK plutonium workers gave estimates of organ retention of ^{239}Pu significantly higher when based on urinary data with the Jones urinary excretion function compared with direct measurements of concentrations in systemic

tissues obtained at autopsy (*para.* (76); Riddell et al., 2000). The Jones function substantitially underestimated urinary plutonium data from injection studies, while these data are overall well reproduced by the more recent plutonium models used in *Publications* 67 and *141* (ICRP, 1993, 2019) and in MWDS-2013 (Birchall at al., 2017a). The latter models also accurately describe the partitioning between urine and total amount going to liver+skeleton (Leggett et al., 2005).

(91) As mentioned in *para* (63) and (76), because of the re-use of adventiously contaminated glass sample bottles in Sellafield, urine data obtained before 1971 were a major source of uncertainty on dose assessment, up to a factor of 10 (Bailey et al., 1996). Organ doses based on these pre-1971 data were therefore largely unreliable.

(92) As described earlier, the HRTM divides the lung into three regions; the bronchial region (BB), the bronchiolar region (bb) and the alveolar-interstitial (AI) region. Where a single quantity is required to represent lung dose a 'detriment-weighted absorbed dose' to the lung was calculated in MWDS-2013 with the weighting scheme of the HRTM (ICRP, 1994a, 2015) – see para. (50) of section 2.2.2. In deriving, apportionment factors representing the region's estimated sensitivity relative to that of the whole lung, *Publication 66* (ICRP, 1994a) considered applying the relative risk concept. In this concept, it is assumed that the induction of cancer by radiation exposure is proportional to the background lung cancer rates. The current information on the relative distribution of the major histological types of lung cancer in populations of smokers and non-smokers suggest a higher cancer incidence in the central airways (BB and bb) compared with the AI region. The regional distribution of lung cancer types in the general population was considered in *Publication 66* (ICRP, 1994a). Values of 0.6 for the BB region, 0.3 for bb region and 0.1 for the AI region are obtained for a population of non-smokers and smokers. Results from experimental animal studies also generally indicate that uniform irradiation of the lung is more likely to lead to the induction of cancer in the BB and bb regions than in the AI region. However, in animal studies in which inhaled insoluble alpha emitters delivered most of the dose to the deep lung, carcinomas appeared to originate in the lung periphery, corresponding to the AI region (ICRP, 1994a). The Commission concluded that there is no quantitative basis for deriving factors, with any acceptable degree of confidence, to represent regional differences in radiation sensitivity among the three regions of the lung: BB, bb, AI. In the absence of such adequate quantitative information, *Publication 66* (ICRP, 1994a) recommended that the BB, bb and AI regions each be assigned one-third of the total radiation detriment in the lung. As the mass of the target tissues in the BB (~ 1 g) and bb (~ 2 g) regions is much smaller than the mass of the AI region (1100 g), this implies far greater sensitivity per unit mass for the central airways than lung tissue of the AI region. The identification and the localisation of radiosensitive target cells in each region of the lung, as well as the combination of regional lung doses into a single dose quantity are additional sources of uncertainty in lung dosimetry.

(93) Saccomanno et al. (1996) studied the distribution of tumours in the bronchial tree for a cohort of 467 miners and 311 non-miners. All subjects were male with positive smoking histories. The results gave the following distributions of tumours in the BB:bb:AI regions as (0.68:0.15:0.16) for miners and (0.59:0.18:0.23) for non-miners. Winkler-Heil et al. (2015) also estimated values of apportionment factors by comparing different radon and thoron exposures, which produce different regional dose distributions, with observed regional cancer distributions. The authors concluded that apportionment factors of ~ (A_{BB} = 0.65, A_{bb} = 0.30, A_{AI} = 0.05) may represent a realistic estimate.

(94) Table 2.1 shows the regional absorbed doses and the detriment-weighted absorbed dose to the lung arising from the inhalation of ^{239}Pu for nitrates and oxides. These values were

calculated using the MWDS-2013 assuming the Commission default apportionment factor (A_{BB}:A_{bb}:A_{AI}) values of (⅓: ⅓: ⅓) and the default model parameter values given by Birchall et al. (2017a). However, assuming apportionment factors of ~ (0.6:0.30:0.1) instead of the Commission default values (⅓: ⅓: ⅓) decreases the detriment-weighted absorbed dose to the lung per unit intake by about 1.5 and 2.2 for plutonium nitrates and oxides respectively.

Table 2.1. Committed absorbed doses to regions of the lung and their relative contribution to the detriment-weighted absorbed lung dose[(a)] arising from the inhalation of 1 Bq of ^{239}Pu for nitrates and oxides[(b)]. Doses are committed over 50 years.

Region/target tissue or organ	Plutonium nitrate		Plutonium oxide	
	Absorbed dose (μGy Bq^{-1})	Fractional contribution[(c)]	Absorbed dose (μGy Bq^{-1})	Fractional contribution[(c)]
Bronchial secretory cells (D_{sec})	0.63		0.24	
Bronchial basal cells (D_{bas})	0.97		0.77	
Bronchial (D_{BB} = 0.5 D_{sec} + 0.5 D_{bas})	0.80	11%	0.51	3%
Bronchiolar (D_{bb})	2.3	32%	2.5	17%
Alveolar interstitial (D_{AI})	4.2	57%	12	80%
Detriment-weighted absorbed lung dose[(a)]	2.4		5.1	

(a) Regional doses were weighted by their relative sensitivity to radiation induced cancer (i.e. by their apportionment factors: A_{BB}=1/3, A_{bb}=1/3, A_{AI}=1/3).
(b) Calculations were carried out with the MWDS-2013 with the default model parameter values given by Birchall et al. (2017a).
(c) Fractional contribution to detriment-weighted absorbed lung dose.

(95) The radiosensitive cells in the central airways are considered to be basal (BB_{bas}) and secretory (BB_{sec}) cells in the bronchial epithelium, and Clara cells (a type of secretory cell) in the bronchiolar epithelium (ICRP, 1994a, 2015b). Based primarily on the histological measurements of Mercer et al. (1991), these radiosensitive targets of the BB and bb regions are assumed to be restricted to tissue layers of given depths and thicknesses. For example, in the BB region, the secretory cells are assumed to be uniformly distributed within the depth range of 10 μm to 40 μm and the basal cells within the range of 35 μm to 50 μm from the lumen. In contrast, the histological measurements of Robbins et al. (1990) showed smaller cell depths with an average secretory and basal cell depths of 19 μm and 27 μm respectively (ICRU, 2012). Mercer et al. (1991) also showed that the cell nuclei were not uniformly distributed but exhibited a distinct maximum within the reported ranges. Thus, the assumed cell depth distribution of the target cells in the central airways is a source of uncertainty.

(96) For plutonium oxide, the dose to the basal cell layer mainly arises from the activity sequestered by macrophages in the lamina propria of the BB region (Birchall et al., 2010; Table 2.1). Thus, the sequestered activity is assumed to be physically closer to the basal cell layer compared with activity deposited on the surface of the epithelium that is cleared quickly by mucociliary action. For plutonium nitrates, the dose to the basal cells arises mainly from both the sequestered activity and the bound activity that is assumed to be uniform throughout the epithelium. Assuming smaller basal cell depths would increase the alpha dose to the basal cell region from activity on the epithelium surface. However, because this lumenal activity is

cleared relatively rapidly, the cell depth distribution of the target cells in the central airways is not a major source of uncertainty for plutonium dosimetry.

(97) Any difference between the actual microdistribution of plutonium in human organs and that assumed by dosimetric models can still be a significant source of uncertainty. For the Mayak workers, a high plutonium burden was observed in the respiratory tract relative to that in systemic tissues at long times after intake. Hahn et al. (2004) investigated by autoradiography the distribution of plutonium in the lungs of 24 autopsied Mayak workers. The concentration of plutonium activity was not uniform in the various lung regions: it was significantly less than the average lung concentration in the bronchovascular interstitial tissue of the bronchi and the lumen of the conducting airway, and significantly higher in parenchymal and nonparenchymal scars, with a density of particles about 14 times the average of the lung. Similarly, Nielsen et al. (2012) observed long-term retention of plutonium in an autopsied Hanford worker (USTUR Case 0269 mentionned above) to be concentrated in parenchymal scar tissue. Some of the fixed deposit of plutonium in the respiratory tract may therefore correspond to plutonium encapsulated in scar tissue. When this occurs, it introduces another source of uncertainty as the HRTM does not take account of such a process. Furthermore, it is not known whether plutonium encapsulated in scar tissue plays a part in lung carcinogenesis. However, lung cancers may develop from scars and fibrosis resulting from injuries in the AI region (Spencer, 1982, 1985; Yu et al., 2008; Kato et al., 2018). In rats, pulmonary fibrosis also appeared to prolong the retention of plutonium dioxide in the lung, without noticeably changing the risk of lung tumor incidence per unit of dose (Lundgren et al., 1991).

2.3. Epidemiological studies

(98) The most important cohort regarding the health effects of plutonium exposure is the Mayak Worker Cohort (MWC), because of the numbers of workers exposed and the magnitude of the exposures. This cohort and the results obtained are detailed in section 2.3.1. Several other studies have been conducted, mainly in the UK and the USA. These studies and the results obtained are detailed in section 2.3.2.

(99) Most of the analyses considered specifically the risk of lung cancer, so particular attention is given to lung cancer, but results related to bone cancer, liver cancer, leukaemia and other cancers are also considered.

2.3.1. Mayak Workers

2.3.1.1. Description of the cohort

(100) The Mayak nuclear complex began operations in 1948 with its mission to produce plutonium for the Soviet Union's nuclear weapons program. Workers at the Mayak facility were exposed to both external radiation and to plutonium (and to some other radionuclides), and received doses that were considerably higher than those from similar operations in other countries.

(101) The Mayak Worker Registry was established in the mid-1980s and initially included workers in the reactors, radiochemical plant, and plutonium production plant hired in the period 1948-1972. The cohort has subsequently been expanded to include workers hired in the period 1973-1982, and workers in auxiliary plants (water treatment and mechanical repair) who were added to expand the number of workers with relatively low doses. The registry includes 25,757 workers with data on occupational history, date and place of birth, vital status (known for 94%

of workers), and date and cause of death (Koshurnikova et al., 1999). By the end of 2008, 12,338 workers had died.

(102) The registry includes estimates of annual doses to several organs/tissues of the body from external gamma irradiation, based on film badge data, and from internally deposited plutonium, based on urine measurements. A limitation of the cohort is that only about 40% of those who worked in the radiochemical and plutonium plants (and thus had potential for non-trivial plutonium exposure) have the urine measurements needed for internal dose estimation. Since the Mayak Worker Registry was established, both external and internal dose estimates have been substantially improved resulting in several dosimetry systems as discussed above in section 2.3 and in Annex A. The mean estimated lung dose among 6540 workers with positive plutonium exposures (plutonium detected in their urine samples) was 0.12 Gy (Gilbert et al., 2013).

(103) The plutonium dose-response relationship has been evaluated for cancers of the lung, liver and bone, the principal organs/tissues of plutonium deposition, and for leukaemia, originating in the red bone marrow adjacent to bone surfaces.

2.3.1.2. Statistical methods

(104) The Mayak worker study is a cohort study and most analyses have been cohort-based with workers followed from the date of their initial employment at Mayak through to the selected end-of-follow-up date. Variables such as attained age, time since exposure, and cumulative doses are allowed to change as workers are followed over time, and are thus considered as time-dependent variables. Analyses rely on internal comparisons in which lung cancer risks are compared by levels of external and internal cumulative dose to the lung, rather than comparisons with an external group, such as the Russian general population. Cumulative lung doses are typically lagged by 5 years; that is, at a time t, doses received in the preceding 5 years are excluded, to account for the minimum latent period for lung cancer. Most analyses are based on an ERR model with the effects of both external and plutonium dose evaluated simultaneously. The ERR model is expressed as follows:

$$\text{Baseline risk } [1 + \text{ERR}_{\text{plutonium}} + \text{ERR}_{\text{external}}].$$

(105) where $\text{ERR}_{\text{plutonium}}$ is a function of cumulative lung dose from plutonium and (possibly) other factors such as sex or age, and $\text{ERR}_{\text{external}}$ is a function of cumulative external doses to the lung and other factors. The excess absolute risk (EAR) has also been evaluated with the hazard of the form

$$\text{Baseline risk} + \text{EAR}_{\text{plutonium}} + \text{EAR}_{\text{external}}.$$

(106) The ERR and EAR were commonly expressed as linear functions of dose, although other functions, such as linear-quadratic and linear-exponential, have also been explored. The baseline risk was either modelled as a function of sex, attained age, and possibly other variables such as smoking; or handled non-parametrically with separate baseline parameters for each stratum defined by these variables. Most recent analyses have assumed a multiplicative relationship for radiation exposure and smoking by including smoking as part of the baseline risk, but departures from a multiplicative relationship have been explored. Models were fitted with either Poisson regression (using the AMFIT module of Epicure) or with Cox regression.

(107) Dose-response analyses for plutonium have been based only on that portion of the data for which plutonium doses could be estimated. Thus, in order to contribute to plutonium dose-response analyses, a worker must either have a plutonium urine measurement or have worked only in the reactor or auxiliary plants where plutonium was not present at a non-trivial extent; these latter workers were considered as unexposed and assigned plutonium doses of zero. Primarily for the purpose of obtaining stable estimates of risk from external dose, some analyses have used a plutonium surrogate based on place and time of employment for workers who were not monitored for plutonium but who had potential for non-trivial exposure, possibly substantial; however, this portion of the data does not contribute to the investigation of the plutonium dose-response relationship.

2.3.1.3. Results by organ

(a) Lung cancer

(108) During the past decade, lung cancer risks from plutonium exposure have been evaluated by several investigators with results published since 1998 summarised in Table 2.2. The earlier lung cancer mortality analyses were based on the Doses-2000 system or earlier dose estimates (Koshurnikova et al., 1998; Kreisheimer et al., 2003; Gilbert et al., 2004), while more recent analyses have been based on Doses-2005 (Jacob et al., 2007; Sokolnikov et al., 2008), MWDS-2008 (Gilbert et al., 2013; Labutina et al., 2013; Zöllner et al., 2015) or MWDS-2013 (Gillies et al., 2017). Labutina et al. (2013) studied lung cancer incidence among workers who died in the city of Ozyorsk, where Mayak is located. The follow-up period for the most recent mortality analysis (Gillies et al., 2017) extends through 2008 (through 2005 for workers who emigrated from Ozyorsk). Historical variations in the number of workers considered in a study are due to different inclusion criteria related to the plant (with or without auxiliary plants) and to the period of exposure (including or not workers hired before 1973). Analyses by Kreisheimer et al. (2003) and Jacob et al. (2007) were restricted to males with smoking data. The most recent analyses excluded workers followed for less than 5 years since many of these workers were lost to follow-up; however, since no lung cancer deaths occurred in this period, this mainly affects the total number of workers reported as contributing to the analysis. Because of differences in the selection of workers, in the follow-up periods and in the consideration of modifying factors of the dose-risk relationship (recent results are presented for an attained age of 60 years), it is difficult to compare estimated ERR per Gy from various analyses.

Table 2.2. Summary of Mayak lung cancer plutonium dose-response analyses published since 1998.

Reference	Workers included in dose-response analyses*	Number of workers (number of lung cancer deaths)		End of follow-up	Dosimetric system	ERR per Gy at age 60 years (95% CI)
		Reactor and auxiliary plants†	Radiochemical and plutonium plants‡			
Koshurnikova et al. (1998)	Males hired in 1948-58	1841 (47)	1479 (105)	1993	Doses-2000	Males: 6.4§ (4.0-9.4)
Kreisheimer et al. (2003)	Males with smoking data hired in main plants 1948-58	2197 (92)	2015 (127)	1999	Doses-2000	Males: 4.5§ (3.2-6.1)
Gilbert et al. (2004)	Males and females hired in main and auxiliary plants 1948-72	7075 (185)	5683 (189)	2000	Doses-2000	Males: 4.7 (3.36.7) Females 19 (9.5-39)
Jacob et al. (2005)	Males with smoking data hired in main plants 1948-72	2086 (105)	2972 (139)	1998	Doses-2000	Did not fit ERR model
Jacob et al. (2007)	Males with smoking data hired in main plants 1948-72	2848 (118)	3445 (183)	2002	Doses-2005	Males: 4.0§ (2.6-8.0)
Sokolnikov et al. (2008)	Males and females hired in main plants 1948-72 and followed for at least 5 years	4155 (149)¶	5341 (215)**	2003	Doses-2005	Males: 7.1 (4.9-10) Females: 15 (7.6-29)

Gilbert et al. (2013)	Males and females hired in main and auxiliary plants 1948-82 and followed for at least 5 years	8081 (233)[¶]	6540 (253)[**]	2008	MWDS-2008	Males: 7.4 (5.0-11) Females: 24 (11-56)
Labutina et al.[††] (2013)	Males hired in main and auxiliary plants 1948-82	90 lung cancer cases[‡‡]	207 lung cancer cases[‡‡]	2004	MWDS-2008	Males: 9.1 (6.0-13.6) Adenocarcinoma: 32[§§] (16-72) Squamous: 3.1[§§] (0.2-9.1) Other epithelial: 4.2[§§] (1.1-11)
Zöllner et al. (2015)	Males hired in main and auxiliary plants 1948-82 with known levels of Pu exposure, smoking status, alcohol drinking habits	8604 (388)		2003 for workers who emigrated from Ozyorsk; 2008 for workers residing in Ozyorsk	MWDS-2008	Non-linear dose response comparable with linear ERR/Gy of 5
Gillies et al. (2017)	Workers hired in main plants, 1948-82	4988 (158)	17,386 (631)	2005 for workers migrated from Ozyorsk; 2008 for workers residing in Ozyorsk	MWDS-2013	Males: 4.74 (3.53-6.24) Females: 11.6 (6.93-18.8)

[*]Workers were either monitored for plutonium or worked only in the reactor or auxiliary plants with little potential for plutonium exposure. Except for Kreisheimer et al, workers with potential for plutonium exposure had to have been monitored at least two years before the end of follow-up.

[†]Little potential for plutonium exposure

[‡]Potential exposure to plutonium

[§]ERR per Gy is for all ages

¶Number with plutonium doses of 0 including a few workers in the radiochemical and plutonium plants

**Number with positive plutonium doses including a few workers in the reactor and auxiliary plants

††Based on cancer incidence data for workers who were diagnosed with lung cancer in the city of Ozyorsk

‡‡The number of workers contributing to these analyses is not given in the paper.

(109) The lung cancer mortality analysis of Gilbert et al. (2013) used MWDS-2008 estimates for internal as well as external doses to the lung. These analyses excluded 1084 workers who either died or were lost to follow-up in the first five years and 10,052 workers (355 lung cancer deaths) who had potential for plutonium exposure but were not monitored for this exposure. The characteristics of the remaining 14,621 (10,918 males and 3703 females) are shown in Table 2.3.

Table 2.3. Number of Mayak workers included in analyses of Gilbert et al. (2013) (percent in parentheses), mean plutonium lung dose, mean external lung dose and number of lung cancers by sex and smoking status.

	All workers	No plutonium dose	Positive plutonium dose*	Mean plutonium dose among those with positive doses* (Gy)	Mean external dose* (Gy)	Lung cancer deaths
Total	14,621	8081	6540	0.115	0.397	486
By sex						
Males	10,918 (75)	6349 (79)	4569 (70)	0.093	0.418	446 (92)
Females	3703 (25)	1732 (21)	1971 (30)	0.165	0.335	40 (8.2)
By smoking status (Males)						
Non-smoker	2518 (23)	1359 (21)	1159 (25)	0.086	0.362	15 (3.4)
Smoker	7027 (64)	3954 (62)	3073 (67)	0.101	0.491	401 (90)
Unknown	1373 (13)	1036 (16)	337 (7.4)	0.045	0.148	30 (6.7)
By smoking status (Females)						
Non-smoker	3052 (82)	1356 (78)	1696 (86)	0.179	0.367	28 (70)
Smoker	111 (3.0)	59 (3.4)	52 (2.6)	0.213	0.384	7 (18)
Unknown	540 (15)	317 (18)	223 (11)	0.053	0.145	5 (13)

* Based on cumulative dose up to 5 years before the end of follow-up

Table 2.4. Distribution of plutonium doses to the lung among 6540 workers with positive doses.*

Dose category (Gy)	Number of workers	Percent	Cumulative percent
>0, <0.1	5452	83.4	83.4
0.1 -	507	7.8	91.1
0.2-	177	2.7	93.8
0.3-	145	2.2	96.0
0.5	128	2.0	98.0
1.0-	62	1.0	98.9
2.0-	55	0.7	99.6
4.0+	25	0.4	100.0

*Based on cumulative lung dose up to 5 years before the end of follow-up

(110) The mean plutonium doses to the lung among exposed females was higher (0.17 Gy) than that for exposed males (0.09 Gy). Seventy-four percent of the 9545 males with smoking data reported smoking, whereas only 3.5% of the 3163 female workers with smoking data reported smoking. Of the 486 lung cancers that had occurred by the end of 2008, 401 were in male smokers. The dose distribution among the 6540 workers with positive plutonium lung

doses is shown in Table 2.4. Only 9% of these workers had plutonium doses exceeding 0.2 Gy and only about 2% had doses exceeding 1 Gy. Nevertheless, the fact that it is not possible to measure the pattern of dose accumulation in individual workers limited the ability to evaluate the potential effects of time since exposure in the Mayak cohort.

(111) Lung cancer mortality was evaluated using ERR models for lung doses from both internal (plutonium) and external exposure with adjustment for attained age, sex, birth cohort, calendar year period, and smoking, with both internal and external doses lagged for 5 years. Fig. 2.1 shows relative risks for lung cancer by plutonium dose category. The ERR for lung cancer was reasonably described by a linear function of internal and external doses. The internal dose ERR was higher for females than males, and declined strongly with attained age. At attained age 60 years, the ERR per Gy for plutonium dose was 7.4 (95% CI 5.0 to 11) for males and 24 (95% CI 11 to 56) for females. A significant dose response was observed when analyses were restricted to plutonium doses to the lung of less than 0.2 Gy ($p < 0.001$), with an estimated ERR/Gy for males at age 60 years of 7.0 (95%CI: 2.5 to 13). This estimate was very similar to that for the full dose range although the confidence interval was wider.

(112) Analyses of 12,708 workers with information on smoking indicated that the interaction of plutonium exposure and smoking was likely to be sub-multiplicative ($p = 0.011$) but greater than additive ($p < 0.001$). The estimated ERR/Gy for smokers was 6.9 (95%Ci: 4.6 to 10), while that for non-smokers was 29 (95% CI: 9.8 to 83). The estimate for non-smokers was based on only 43 lung cancer deaths and thus was highly uncertain. With modification by smoking accounted for, the ERR/Gy estimates for males and females were nearly identical.

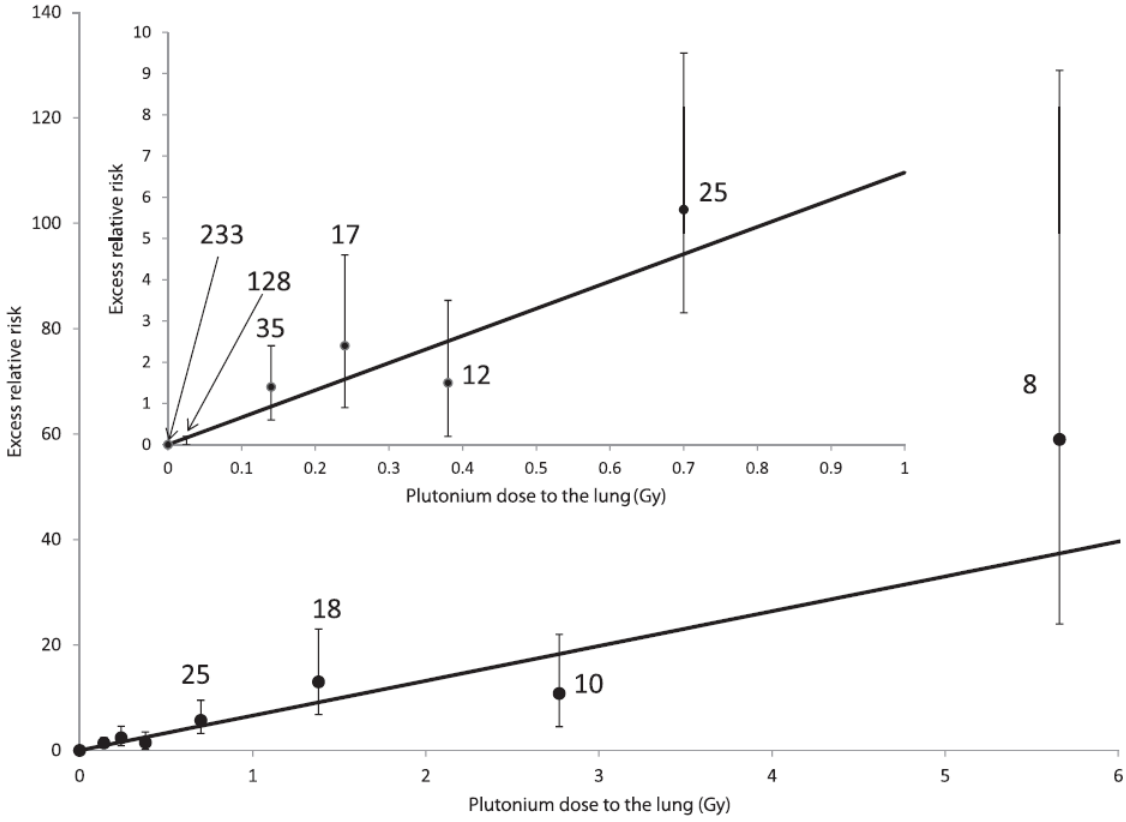

Fig 2.1. Excess relative risk (with 95% CI) of lung cancer and number of lung cancer deaths by categories of plutonium dose to the lung (black points and vertical bars) and fitted linear function, for males at age 60 years (Gilbert et al., 2013).

(113) Labutina et al. (2013) evaluated lung cancer incidence among workers who were diagnosed with lung cancer while resident in Ozyorsk. Importantly, data on histological type of lung cancer were available. Significant dose-response relationships were found for adenocarinoma, squamous cell, and other epithelial lung cancers with a much larger ERR/Gy for adenocarcinomas than those for lung cancer of other types (Table 2.2).

Analysis performed in the SOLO European project

(114) As part of the European Union's FP7 SOLO (epidemiological studies of exposed Southern Urals populations) project, epidemiological studies of the Mayak plutonium workers were conducted, in terms of lung cancer and leukaemia mortality and incidence, and circulatory disease mortality. To make a comparison with lower occupational exposures to plutonium, a parallel study of plutonium workers at the UK Sellafield nuclear complex was also carried out as part of the SOLO project (Gillies et al., 2017). The findings from the SOLO project for lung cancer for the Mayak workers cohort (MWC) are considered below, with the equivalent results for the Sellafield workers cohort (SWC) presented in Section II.3.2.2.

(115) The MWC consisted of 22,374 radiation workers first employed at the main plants during 1948-1982, of whom 6989 were monitored for exposure to plutonium and 10,397 were potentially exposed to plutonium (possibly heavily) but were not monitored for this exposure; monitoring for exposure to plutonium at Mayak through urinalysis started around 1970. The period of follow-up was terminated at the end of 2008 for Mayak workers who were residents of Ozyorsk, and at the end of 2005 for Mayak workers who had emigrated from Ozyorsk.

(116) Overall, there were 789 deaths from lung cancer in the MWC, but only 509 lung cancer incidences were observed due to the restriction of the incidence analysis to residents of Ozyorsk. Among those monitored for plutonium exposure there were 267 incident cases of, and 253 deaths from, lung cancer (when workers diagnosed with lung cancer within two years of first monitoring for plutonium were excluded because of the possibility that monitoring may have occurred because of concerns about the health of a worker). Information on smoking status was not available for this analysis because of the lack of information for Sellafield workers comparable to that available for Mayak workers.

(117) The ERR with respect to radiation dose to the lung, from both external gamma radiation and internal alpha radiation from plutonium, was estimated taking into account all of the available non-radiation factors: those affecting background rates were sex, attained age and birth cohort, while those affecting the radiation risk estimates were sex and attained age.

(118) Uncertainty surrounding the choice of the slow dissolution rate (s_s) for plutonium nitrate in lung meant that two sets of lung doses from plutonium were generated for use in the analyses: that derived from Mayak autopsy cases ($s_s = 2.5 \times 10^{-4}$ d^{-1}) and that derived from UK volunteer experiments ($s_s = 2.2 \times 10^{-3}$ d^{-1}) (see details in Section 2.2.3).

(119) Lung cancer mortality and incidence were found to be significantly increased at relatively high lung doses from plutonium (for mortality, >200 mGy using $s_s = 2.5 \times 10^{-4}$ d^{-1} and >100 mGy using $s_s = 2.2 \times 10^{-3}$ d^{-1}; for incidence, >200 mGy using $s_s = 2.5 \times 10^{-4}$ d^{-1} and >50 mGy using $s_s = 2.2 \times 10^{-3}$ d^{-1}). As in previous studies of Mayak workers, the plutonium dose-response for lung cancer incidence among male Mayak workers was found to be linear across the whole dose range with ERR/Gy estimates of 7.88 (90% CI: 5.73, 10.65) using $s_s = 2.2 \times 10^{-3}$ d^{-1} and 5.27 (90% CI: 3.83, 7.12) using $s_s = 2.5 \times 10^{-4}$ d^{-1}, at an attained age of 60 years, while for lung cancer mortality among male Mayak workers the ERR/Gy estimates were 7.02 (90% CI: 5.23, 9.23) using $s_s = 2.2 \times 10^{-3}$ d^{-1} and 4.74 (90% CI: 3.53, 9.23) using $s_s = 2.5$

× 10^{-4} d^{-1}, at an attained age of 60 years. The ERR/Gy point estimates were found to be consistent down to a relatively low lung dose when restricting the range of plutonium dose included in the analysis. For example, in the incidence analysis for Mayak males a significant ERR/Gy estimate was detectable down to 0.05 Gy, and for the mortality analysis for Mayak males a significant ERR/Gy estimate was detectable down to 0.1 Gy, these estimates being positive and consistent with those for the full dose range.

(120) For Mayak female workers, the ERR/Gy at 60 years of age in terms of lung dose from plutonium was, for lung cancer mortality, 11.62 (90% CI: 6.93, 18.78) for $s_s = 2.5 \times 10^{-4}$ d^{-1} and 16.11 (90% CI: 9.60, 26.02) for $s_s = 2.2 \times 10^{-3}$ d^{-1}, while for lung cancer incidence, 20.41 (90% CI: 11.47, 36.04) for $s_s = 2.5 \times 10^{-4}$ d^{-1} and 27.55 (90% CI: 15.44, 48.61) for $s_s = 2.2 \times 10^{-3}$ d^{-1}.

(121) Gillies et al. (2017) examined the effect of external irradiation upon lung cancer risk in the Mayak workforce. For lung cancer mortality, the ERR/Gy (using the $s_s = 2.5 \times 10^{-4}$ d^{-1} solubility assumption) was 0.38 (90% CI: 0.22, 0.58), while for lung cancer incidence it was 0.30 (90% CI: 0.12, 0.54); the risk estimates obtained using the $s_s = 2.2 \times 10^{-3}$ d^{-1} solubility assumption were little different.

(b) Liver cancer

(122) Dose-response analyses utilising the Mayak Doses-2005 system were reported by Sokolnikov et al. (2008) with a linear function providing an adequate fit. The ERR/Gy for plutonium dose to the liver differed significantly by sex, and was 2.6 (95% CI: 0.7 to 6.9) for males and 29 (95% CI: 9.8 to 95) for females. The association was only apparent for plutonium liver doses in excess of 3 Gy. There was no evidence that the ERR/Gy depended on attained age.

(c) Bone cancer

(123) Sokolnikov et al. (2008) reported a significant dose-response for bone cancer based on bone surface doses from Doses-2005. However, the evidence for a bone cancer dose-response relied on only three deaths with doses exceeding 10 Gy under the Mayak Doses-2005 system. The doses for these workers under Doses-2005 were 18 Gy (male), 31 Gy (female) and 69 Gy (female). All three deaths occurred before age 55 years.

(d) Leukaemia

(124) Shilnikova (2003) conducted analyses of cancer mortality in the cohort of about 21,500 workers hired at the main and auxiliary plants between 1948 and 1972. Plutonium body burden estimates were used for monitored workers and a surrogate index of plutonium exposure was used for unmonitored workers. The analyses for leukaemia mortality indicated a clear dose-response relationship for external dose, but there was no evidence of a dose-response for plutonium dose.

(125) Leukaemia incidence risk among 22,373 Mayak workers was analysed by Kuznetsova et al. (2016). Leukaemia risk clearly depended on the dose from external exposure, but showed no significant response to the dose from plutonium-emitted alpha-particles to the bone marrow or a raised risk in unmonitored workers from the most hazardous plutonium facilities in the early years of operations at Mayak.

(126) Although leukaemia mortality and incidence in the Mayak and Sellafield workforces was part of the EU SOLO study, the results of the leukaemia component of this study have yet to be published.

(e) Other cancers

(127) Cancer incidence was analysed to investigate the association between doses from external gamma-ray and internal plutonium exposures and solid cancers risk other than lung, liver and bone cancers (cancer sites strongly related to plutonium deposition) (Hunter et al., 2013). The MWC included 22,366 workers first employed between 1948 and 1982. A total of 1447 cases of other solid cancers were registered in the follow-up period until 2004. A weak association was found between cumulative dose from external gamma rays and the incidence of solid cancers other than lung, liver and bone (ERR/Gy = 0.07; 95% CI: 0.01–0.15), but this association lost its significance after adjusting for internal plutonium dose (ERR/Gy = 0.06; 95% CI: -0.01, 0.14). There was no significant association with plutonium liver dose (ERR/Gy = 0.10; 95% CI: -0.02, 0.26) or with potential plutonium exposure in unmonitored workers. The authors concluded that their analysis did not provide evidence of an increased risk of plutonium exposure for solid cancers other than lung, liver and bone cancers (Hunter et al., 2013).

(128) Mortality from solid cancers other than lung, liver and bone was analysed by Sokolnikov et al. (2015a). The cohort under study included 25,757 workers from main (reactor, radiochemical and plutonium production) as well as auxiliary (water treatment and mechanical repair) plants. The analyses used the MWDS-2008 and an extended follow-up until 2008. Using an ERR approach it was demonstrated that a linear dose-response with exposure to external gamma rays provided the best fit to the data: ERR/Gy = 0.16 (95% CI: 0.07, 0.26) when unadjusted for plutonium exposure and ERR/Gy = 0.12 (95% CI: 0.03, 0.21) when adjusted for plutonium dose and monitoring status. Cancer of the oesophagus was notably raised in relation to external dose: ERR/Gy = 1.26 (95% CI: 0.36, 3.27). The background of other solid cancer mortality rate was clearly higher among those who had been monitored for plutonium (RR 1.16, 95% CI 1.11 – 1.39) compared to workers not monitored for plutonium, and when this difference with respect to monitoring status was taken into account, the dose response using plutonium liver dose was not statistically significant. The authors concluded that while there was some evidence of an excess risk associated with inhalation of ^{239}Pu for mortality from solid cancers other than lung, liver or bone, this may have been largely due to factors related to the selection of subjects for plutonium monitoring (Sokolnikov et al., 2015a). A subsequent study (Sokolnikov et al., 2017) found no evidence that exposure to plutonium aerosols significantly affected the risk associated with external exposure.

2.3.2. Other Plutonium Worker Cohorts

2.3.2.1. Description of epidemiological studies

(129) Table 2.5 summarises the characteristics of the cohort and case-control studies allowing quantification of cancer risks based on individual estimates of plutonium exposure, using measurements or job-exposure matrices.

1373 Table 2.5. Summary of studies of occupational exposure to plutonium and cancer among workers other than the Mayak workforce.

Reference	Country, Site	Type of Study	Health Indicator	Type of Work	Population Characteristics	Person-Years (mean duration of follow-up)	Exposure monitoring	
							External	Internal
Omar et al. (1999)	UK Sellafield	Cohort	Mortality/ Incidence	Production and nuclear fuel reprocessing and storage (Pu alpha, ^{241}Pu, ^{241}Am)	10,382 monitored for external or internal radiation (5203 monitored for Pu) 3937 never monitored (19% female)	415,432 (29.0)	Recorded exposure	Urine measurements for Pu
Wing et al. (2000)	US Hanford, Los Alamos/Zia, Oak Ridge National Lab, Savannah River	Case-Control Multiple Myeloma	Mortality	Nuclear sites with potential for external exposure, absence of major dust exposure (Pu, Sr, ^{3}H)	98 cases, 391 controls matched on age at death (18% female)	n.a.	Recorded exposure to gamma, neutrons; missing doses assumed unexposed	Urine/faecal bioassays for U, Pu Sr, tritium; WBC
Brown et al. (2004)	US Rocky Flats	Case-Control Lung Cancer	Mortality	Chemical processing to Pu metal via Pu oxide; Pu rolling and machining (^{238}Pu, ^{239}Pu, ^{241}Pu, ^{241}Am, ^{234}U, ^{238}U)	180 cases, 720 controls matched on age, sex, birth year	n.a.	Recorded exposure to gamma, neutrons; missing doses imputed	Urine measurements for Pu, U; lung counts of Pu, U; ^{241}Am as fraction of ^{239}Pu and ^{241}Pu intake
McGeoghegan et al. (2003)	UK Sellafield	Cohort	Mortality/ Incidence	Pu by production and nuclear fuel reprocessing and	Female workers: 837 plutonium workers, 1587 other rad workers, 3194 non-rad workers	142,337 (22.3)	Recorded exposure at site plus other sites	Urine measurements for Pu

Reference	Country, Site	Type of Study	Health Indicator	Type of Work	Population Characteristics	Person-Years (mean duration of follow-up)	Exposure monitoring	
							External	Internal
				storage (Pu alpha, ^{241}Pu, ^{241}Am)				
Atkinson et al. (2004)	UK UKAEA	Cohort	Mortality	Production and nuclear fuel reprocessing and storage (Pu-alpha, ^{241}Pu, ^{241}Am)	51,367 (29% female) Age at entry (29.0)	1,371,153 (26.7)	Recorded exposure to x, gamma neutrons, tritium at site plus other sites	Record indicating internal radiation monitoring - any, Pu
Wing et al. (2004); Wing and Richardson (2005)	US Hanford	Cohort	Mortality	Pu chemical separation and fuel fabrication, nuclear reactor research and development	3066 routine Pu exposure 8266 non-routine Pu exposure 15,058 unexposed	n.a.	Recorded exposure to gamma and tritium at site; missing doses imputed	In vivo monitoring Y/N; Pu worker with routine exposure, non-routine exposure, unexposed based on job title, work area, and time period
Schubauer-Berrigan et al. (2007)	US Hanford, Los Alamos/Zia, Oak Ridge National Lab,	Case Control Chronic myeloid and acute	Mortality	Nuclear sites with potential for external exposure, absence of major dust exposure (Pu)	206 non-CLL leukaemia cases, 823 controls	n.a.	Recorded exposure to photons, tritium, neutrons at site and other sites;	Urine monitoring for Pu

Reference	Country, Site	Type of Study	Health Indicator	Type of Work	Population Characteristics	Person-Years (mean duration of follow-up)	Exposure monitoring	
							External	Internal
	Savannah River, Portsmouth Naval Shipyard	leukaemia					occupational medical x-rays	
Gillies and Haylock (2014)	UK Sellafield	Cohort	Mortality/ Incidence	external radiation workers, internal radiation workers and non-radiation workers	64,956 workers employed between 1946 and 2002, followed up to 2005	1,894,069	personal dosimeters, usually film badges	Any biological sample for Pu, U or ^{3}H monitoring
Gillies et al. (2017)	UK Sellafield	Cohort	Mortality/ Incidence	Production and nuclear fuel reprocessing and storage (alpha, ^{241}Pu, ^{241}Am)	23,443 workers employed by BNFL, UKAEA or the MoS between 1947 and 2002 who were ever employed at the Sellafield site and have been monitored for radiation exposure	602,311 (25.7)	Regular monitoring based on individual film badges; archived data adjusted to account for historical practices and converted to organ doses	Regular urine monitoring for Pu for all persons who worked in areas where contact with Pu was possible

Reference	Country, Site	Type of Study	Health Indicator	Type of Work	Population Characteristics	Person-Years (mean duration of follow-up)	Exposure monitoring	
							External	Internal
Grellier et al. (2017)	Europe UK (BNFL, AWE, UKAEA), France (CEA, AREVA), Belgium (SCK-CEN, Belgo-nucléaire, Belgoprocess)	Case Control Lung cancer	Mortality	Nuclear research, waste treatment, fuel production/ reprocessing, construction/ operation of experimental reactors, nuclear weapons production (alpha, Pu, U)	Workers employed for at least 1 year and monitored for internal exposure to Pu and/or U through urinalysis 553 cases / 1333 controls	n.a.	Individual annual external dose estimates based on personal dosimeters	Doses reconstructed from bioassay data (urinalysis, fecal analysis, in vivo monitoring) using a common methodology

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UK studies

(130) The studies of Omar et al. (1999), McGeoghegan et al. (2003) and Gillies and Haylock (2014) reported on cancer mortality and incidence among Sellafield workers. Omar et al. (1999) included 14,319 male and female workers. They classified 5203 workers as plutonium workers because urine samples for plutonium monitoring were available for them, among which there were 839 females. Two methods were used to assess plutonium uptake for these workers: individual assessments and standard assessments. For the 993 workers involved in an exposure incident or compensation claim, individual assessments were done by a health physicist using urine assays, full work history records and the circumstances of known acute exposure incidents. Standard assessments were done for 3616 workers using urine assays and assuming plutonium exposure started 6 months prior to the date of first urine sample and ended on the date of the last sample. No assessment was done for the remaining 594 workers who were known to have been potentially exposed to plutonium but had limited or no usable urine data. Organ/tissue doses were calculated for the 4609 workers with adequate plutonium urine monitoring records; these plutonium doses were added to external doses in the analyses of trends of risk with cumulative dose, but separate analyses in terms of plutonium dose only were not conducted. McGeoghegan et al. (2003) restricted their study to 5618 female workers of whom 837 were identified as plutonium workers. Among these 837 women, 643 had at least 5 urine samples so that estimates of assessed organ/tissue-specific plutonium doses could be calculated. Detectable plutonium burdens were found for 360 workers. A detailed description of how the organ/tissue-specific plutonium doses were calculated for the Sellafield workers can be found in Section 2.2.4. Gillies and Haylock (2014) calculated SMRs for 12,272 Sellafield workers monitored for exposure to plutonium and followed up to the end of 2005. For these Sellafield worker studies, the SMRs for plutonium workers were calculated and also compared to those for other Sellafield workers.

(131) Atkinson et al. (2004) studied mortality among 51,397 UKAEA workers. The effect of plutonium exposure was evaluated by stratifying workers into ever/never monitored for plutonium based on the presence or absence of records documenting a worker being monitored for plutonium exposure. Cumulative external radiation exposure included exposure at the study site plus other sites when the exposure was known and occurred prior to employment at the site. In addition, the external exposure measures included tritium and neutron exposures and were adjusted for sub-threshold and missing readings. Plutonium-specific doses were not calculated.

(132) The Sellafield worker cohort has also been analysed in the framework of the European Union SOLO project (Gillies et al., 2017) to study lung cancer and leukaemia mortality and incidence, and circulatory disease mortality, in the Mayak and Sellafield workforces. The SWC consisted of 23,443 radiation workers first employed during 1947-2002, of whom 12,192 were ever monitored for exposure to plutonium, including 1815 women. The period of follow-up was terminated at the end of 2005. Overall, there were 384 incident cases of, and 406 deaths from, lung cancer in the Sellafield workers. Among those monitored for plutonium exposure there were 220 incident cases of, and 225 deaths from, lung cancer. The ERR with respect to radiation dose, from both external gamma radiation and internal alpha radiation to the lung from plutonium, was estimated taking into account all of the available non-radiation factors: those affecting background rates were sex, attained age and birth cohort, while those affecting the radiation risk estimates were sex and attained age. Uncertainty surrounding the choice of the lung solubility parameter for plutonium nitrate led to two sets of lung doses from plutonium

being generated for use in the analyses: that derived from Mayak autopsy cases ($s_s = 2.5 \times 10^{-4}$ d^{-1}) and that derived from UK volunteer experiments ($s_s = 2.2 \times 10^{-3}$ d^{-1}). The leukaemia component of the SOLO study has yet to be reported.

US studies

(133) The cohort study of 26,389 Hanford workers employed for at least six months during 1944-1978 (Wing et al., 2004) focused on mortality and length of employment in jobs with potential for plutonium exposure. Deaths before 1995 were identified. A job-exposure matrix was used to stratify each year of a worker's employment into one of 3 categories of potential for plutonium exposure: minimal, non-routine and routine. The 3-dimensional matrix was developed using facility information on job title, area/process and time period. The records for the 377 workers (1.4% of the workers studied) with documented systemic plutonium deposition were used to test the ability of the matrix to identify workers with documented contamination. The average length of follow up exceeded 22 years for the three groups where this information was available. Although these three groups are relatively large, the number of workers identified as exposed to plutonium was considerably less: among Hanford workers 3065 individuals were identified as routinely exposed and 8266 as non-routinely exposed.

(134) Wiggs et al. (1994) studied 15,727 white males employed for any length of time at Los Alamos during 1943-1977 and examined mortality rates to the end of 1990, particularly in relation to cumulative systemic plutonium deposition calculated from urinalysis results. The 303 workers with a cumulative systemic plutonium deposition ≥74 Bq (when lagged by 10 years) were compared to 3472 workers with plutonium depositions <74 Bq. Voelz et al. (1997) studied 26 workers who were employed in the Manhattan Project at Los Alamos during 1944-1945, and were highly exposed to plutonium.

(135) Wilkinson et al. (1987) studied 5413 white males employed for at least two years at Rocky Flats during 1952-1979. They examined mortality to the end of 1979, particularly in relation to cumulative systemic plutonium deposition calculated from urinalysis results. Mortality rates for workers with cumulative systemic plutonium depositions (lagged by 10 years, or two years for leukaemia) <74 Bq were compared with rates for workers with depositions ≥74 Bq, and for all cancers and lung cancers for depositions 74-184 Bq and ≥185 Bq.

(136) Three case-control studies conducted in the US considered various cancer outcomes. Wing et al. (2000) studied 98 cases (and 391 matched controls) of multiple myeloma mortality among workers hired before 1979 at four U.S. nuclear facilities (Hanford, Los Alamos, Oak Ridge and Savannah River) with a potential for external exposure and an absence of major radioactive dust exposure. Cause of death before 1991 (1987 for Hanford) was identified in a total of 115,143 workers. Bioassays of urine and faecal samples and whole-body counting records were used to stratify workers according to monitoring for internal radiation exposure, which included plutonium, uranium, strontium, and tritium. External exposure estimates included tritium and neutrons.

(137) Schubauer-Berigan et al. (2007) conducted a case-control study of leukaemia excluding chronic lymphocytic leukaemia (non-CLL leukaemia) mortality (206 cases and 823 controls) among workers at the same four U.S nuclear facilities as Wing et al. (2000) plus the Portsmouth Naval Shipyard. Cause of death before 1995 (1997 for Portsmouth) was identified among a total of 94,517 workers employed for at least 30 days before 1979 or 1978 (1975 for Savannah River) and monitored for exposure to radiation. Bone marrow doses were determined for each study member using external radiation exposure to photons, neutrons and tritium;

occupational medical x rays; and plutonium urine measurements. Urinary excretion data were used to estimate potential systemic plutonium deposition. Four categories were defined based on the highest reading of plutonium excretion measured in mBq d^{-1}. Over half the cases (58%) and controls (54%) had no available bioassay records. Bone marrow doses were calculated using current ICRP biokinetic models and default parameters. Three assumptions were made: inhalation was the route of entry, intakes occurred 3 days before the first associated positive bioassay sample, and the solubility of the inhaled material was 50% Type M and 50% type Y (Daniels et al., 2006).

(138) In their lung cancer mortality nested case-control study of 180 cases and 720 matched controls among 16,258 Rocky Flats workers employed for at least six months during 1952-1989, Brown et al. (2004) calculated dose to the lung using recorded external exposure to gamma radiation and neutrons, urine bioassays for uranium and plutonium, and lung counts for plutonium and uranium and their decay products, and inferred doses from ^{241}Am. For external doses, gamma and neutron doses were recorded as a combined dose. Missing doses for one or more years were imputed for 51.7% of cases and 58.9% of controls. For internal doses, effective intakes and annual equivalent doses were estimated using Code for Internal Dosimetry, version 1.3 which was based on *Publication 30*. Smoking histories were obtained from interviewing relatives (80% of histories), medical records and co-worker interviews; smoking information was obtained for 68% of cases and 84% of controls.

Combined analysis of Mayak and Sellafield Plutonium Workers (European Union SOLO project)

(139) To date, evidence of lung cancer and other cancer risks in relation to plutonium exposure have been mostly based on findings on the MWC. However, the scale of the exposures and the different dose assessment methodology used in the MWC meant that there was considerable uncertainty about whether the risks derived from this cohort could be extrapolated to low doses and were applicable to other cohorts. The SWC represents one of the few available companion cohorts with individual plutonium monitoring data available over a long follow-up period, with around 500,000 urine sample results available for over 12,000 plutonium monitored workers, covering the low dose range. The MWC and SWC therefore represent complementary resources for studying the health effects associated with plutonium exposure. The combining of these cohorts using a unified dosimetry methodology has enabled the study of plutonium risks over a wider dose range than could be managed in the MWC alone (Gillies et al., 2017).

(140) The combined cohort of Mayak and Sellafield workers includes 45,817 workers hired either in the main facilities of Mayak PA (that is reactor, radiochemical and plutonium production plants) in 1948 – 1982 or at Sellafield in 1947 – 2002. The pooled cohort includes a total of 1195 lung cancer deaths. Levels of plutonium intake in the MWC were much higher, the SWC data contributing mainly to the lower dose range.

(141) Analyses in terms of both lung cancer mortality and incidence were conducted (Gillies et al., 2017). One particular feature of these analyses is that the alpha-particle dose to the lung was calculated twice, using different parameter values describing the rate of plutonium absorption from the lung (as explained in Section 2.3.3). This is due to dosimetry differences between the MWC and the SWC that could not be resolved in the timescale required for the epidemiological analyses.

(142) Smoking information was available for MWC only, and so could not be used in the combined analysis, but from the analysis of the background (i.e. in absence of radiation

exposure) lung cancer mortality rates it was clear that smoking rates in the SWC were lower than in the MWC.

(143) The leukaemia component of the SOLO project has yet to be reported.

European combined analysis of Plutonium Workers (Alpha-Risk European Union project)

(144) In the EU-funded Alpha-Risk project (Bingham et al., 2017; Grellier et al., 2017), lung cancer and leukaemia mortality risks associated with internal exposure to uranium and plutonium were investigated through a case-control study, nested within radiation worker cohorts in the UK (AWE, UKAEA and BNFL cohorts), Belgium (SCK•CEN/Belgonucléaire/Belgoprocess cohort) and France (CEA/COGEMA cohort). The case-control design allowed detailed dose reconstruction as well as the collection of individual data on potential confounders (Grellier et al., 2017).

2.3.2.2. Results by organ system

Lung cancer

(145) Studies of lung cancer risk associated with plutonium exposure (other than Mayak workers) are summarised in Table 2.6.

1529 Table 2.6. Summary of results of epidemiological studies of plutonium exposed populations (other than Mayak workers) for lung cancer risk.

Reference	Health Indicator	Observed Cases	Expected Cases	Mean Cumulative Dose (mSv)	Average ERR At 1 Sv	Other Risk Estimate
Omar et al. (1999)	Mortality	133	145.8	194 (Pu organ dose)	n.a.	no dose response with cumulative plutonium dose plus external radiation
Omar et al. (1999)	Incidence	81	85.5	194 (Pu organ dose)	n.a.	no dose response with cum Pu dose + external radiation
Brown et al. (2004)	Mortality	180 cases	720 controls	210 cases; 388 controls (lung dose)	-0.05 (95% CI -0.23-0.13) all workers; 0.13 (95% CI -0.18-0.43) employed 10-25yrs; 1.14 (95% CI 0.12-2.16) hired 1960-67	statistically significant increased risk cum lung dose ≥400mSv; statistically significant dose-response with cumulative lung dose for employment 15-25 years; no effect with plutonium systemic deposition
McGeoghegan et al. (2003)	Mortality	2	2.00	23.3 external; 3.45 internal lung dose	n.a.	no dose response with cumulative plutonium dose
Wing et al. (2004, 2005)	Mortality	n.a.	n.a.	27.9 external	n.a.	% increase in mortality/year employed in routine plutonium jobs = 2.0 (SE=1.8); age<50 -1.0 (SE=2.7); age 50+ 7.1 (SE=3.4) age <55: 0.14 (90%CI <0-4.82); age 55+: 24.62 (90%CI 6.76-59.02) for external irradiation among plutonium workers.

Reference	Health Indicator	Observed Cases	Expected Cases	Mean Cumulative Dose (mSv)	Average ERR At 1 Sv	Other Risk Estimate
Gillies and Haylock (2014)	Mortality	225	204.8	N/A	N/A	SMR only calculated
Gillies and Haylock (2014)	Incidence	220	198	N/A	N/A	SIR only calculated
Gillies et al. (2017)	Mortality	406	n.a.	Pu organ dose (mGy) $s_s = 2.5 \times 10^{-4}$ d^{-1}, 5.5 $s_s = 2.2 \times 10^{-3}$ d^{-1}, 1.9	$s_s = 2.5 \times 10^{-4}$ d^{-1}: ERR/Gy* = 6.34 (90%CI <–1.6; 18.8) $s_s = 2.2 \times 10^{-3}$ d^{-1}: ERR/Gy* = 20.60 (90%CI <–1.5; 58.6)	External: 0.2 (90%CI –0.3; 0.8)
Gillies et al. (2017)	Incidence	384	n.a.	Pu organ dose (mGy) $s_s = 2.5 \times 10^{-4}$ d^{-1}, 5.5 $s_s = 2.2 \times 10^{-3}$ d^{-1}, 1.9	$s_s = 2.5 \times 10^{-4}$ d^{-1}: ERR/Gy* = 8.14 (90%CI –1.2; 21.2) $s_s = 2.2 \times 10^{-3}$ d^{-1}: ERR/Gy* = 27.00 (90%CI –2.1; 67.6)	External: 0.2 (90%CI –0.3; 0.8)

Reference	Health Indicator	Observed Cases	Expected Cases	Mean Cumulative Dose (mSv)	Average ERR At 1 Sv	Other Risk Estimate
Grellier et al. (2017)	Mortality	553 cases	1333 controls	Pu lung dose 5.1 mGy	EOR/Gy = 50 (90% 17, 106) adjusted for external radiation, socioeconomic status, and smoking	EOR/Gy = 11 (90% 2.6, 24) for total alpha lung dose (Pu+U), adjusted for external radiation, socioeconomic status, and smoking

*at age 60

UK studies

(146) In the studies of Sellafield workers, the healthy worker effect was seen for both mortality and incidence (Omar et al., 1999; McGeoghegan et al., 2003; Gillies and Haylock, 2014). The average lung dose from plutonium was 194 mSv and from the external radiation was 196.7 mSv. No dose response was observed with cumulative plutonium dose plus external radiation for lung cancer mortality or incidence among plutonium workers (Omar, 1999). McGeoghegan et al. (2003) failed to find a dose response with cumulative plutonium dose among female workers.

(147) The EU SOLO project examined lung cancer mortality and incidence in the Sellafield workforce (Gillies et al., 2017); there were 384 incident cases of, and 406 deaths from, lung cancer.

(148) For lung cancer mortality and incidence, there was no consistent pattern of significantly raised risks by plutonium lung dose group for either $s_s = 2.5 \times 10^{-4}$ d^{-1} or $s_s = 2.2 \times 10^{-3}$ d^{-1} dissolution rate, although point estimates of lung cancer ERR were positive for all dose groups for both mortality and incidence for both solubility assumptions. Estimates of ERR/Gy of lung dose from plutonium at age 60 years were non-significantly positive for both lung cancer mortality and incidence: for mortality, ERR/Gy was 6.34 (90% CI: <-1.6, 18.8) for $s_s = 2.5 \times 10^{-4}$ d^{-1} and 20.60 (90% CI: <-1.5, 58.6) for $s_s = 2.2 \times 10^{-3}$ d^{-1}; and for incidence, ERR/Gy was 8.14 (90% CI: <-1.21, 21.17) for $s_s = 2.5 \times 10^{-4}$ d^{-1} and 27.00 (90% CI: <-2.06, 67.6) for $s_s = 2.2 \times 10^{-3}$ d^{-1} (Gillies et al., 2017).

(149) Lung cancer mortality and incidence were also examined with respect to external exposure. For lung cancer mortality, the ERR/Gy was 0.22 (90% CI: -0.25, 0.82) for $s_s = 2.5 \times 10^{-4}$ d^{-1} and 0.18 (90% CI: -0.27, 0.78) for $s_s = 2.2 \times 10^{-3}$ d^{-1}, while for lung cancer incidence, the ERR/Gy was 0.25 (90% CI: -0.23, 0.88) for $s_s = 2.5 \times 10^{-4}$ d^{-1} and 0.22 (90% CI: -0.26, 0.84) for $s_s = 2.2 \times 10^{-3}$. The pattern of these risk estimates was consistent with that obtained for the plutonium alpha-particle dose to the lung in the Sellafield workers: the ERR/Gy estimates were positive, but not significantly so (Gillies et al., 2017).

US studies

(150) In their study of Hanford workers, Wing et al. (2004) focused on workers in jobs with routine potential for plutonium exposure. They found a positive relationship between such jobs and risk of lung cancer: the increase in lung cancer mortality was 2.0% (S.E. = 1.8) for each year employed in a job with routine potential for plutonium exposure. The risk prior to age 50 years was -1.0% (S.E. = 2.7) while the risk for age 50+ years was 7.1% (S.E. =3.4).

(151) Wiggs et al. (1994) studied workers at Los Alamos, particularly in relation to cumulative systemic plutonium deposition. For 303 workers with cumulative systemic plutonium deposition ≥74 Bq (when lagged by 10 years), the mortality rate ratio for lung cancer with respect to 3472 workers with plutonium depositions <74 Bq, was 1.78 (95% CI: 0.79, 3.99). Voelz et al. (1997) found 1 lung cancer death in the 26 Manhattan Project workers highly exposed to plutonium, less than that expected from national rates; the RR when compared to the lung cancer mortality rate among 876 unexposed Los Alamos male workers employed during 1944-1945 was 3.31 (95% CI: 0.44, 25).

(152) Wilkinson et al. (1987) reported a significantly low SMR for lung cancer in the Rocky Flats workforce. The RR when the lung cancer mortality rate in plutonium exposed workers (≥74 Bq systemic deposition) was compared to unexposed workers (<74 Bq) was 1.43 (95% CI: 0.33, 4.65), but the RR in the highest exposed group (≥185 Bq) was 0.63.

(153) Brown et al. (2004) presented results from the lung cancer mortality nested case-control study of Rocky Flats workers. The risk of lung cancer with respect to internal lung dose (lagged by ten years) was reported. Odds ratios (adjusted for cumulative external dose, period of joining and employment duration) were elevated for all five non-zero categories of cumulative internal lung dose, with ORs being greatest for intermediate dose groups and significant for the middle 21-32 mGy category. There was a significant reduction of OR with length of employment duration. The ORs for two non-zero external dose categories were non-significantly less than 1.0. With a further adjustment for the number of years of non-zero internal lung dose (to address uncertainties in the dosimetry methodology) significantly elevated ORs were found for all five internal lung dose categories; there was a significant reduction in OR with increasing number of years of non-zero internal lung dose. Additionally adjusting for age at first estimate of lung dose for those workers with a non-zero internal lung dose reduced the ORs so that none was statistically significant, but the effect of age at first hire was significant (OR=1.05, O=98, 95%CI 1.01-1.10); this adjustment for age at first internal lung dose had the effect of notably increasing the ORs for the external dose categories, but neither OR was significantly different from 1.0. A statistically significant positive linear trend with internal lung dose was found for workers employed for 15-25 years ($p<0.001$), but for those workers employed for <15 years or for >25 years ORs for most internal lung dose categories were less than 1.0 and none was significant. Brown et al. (2004) state that the inclusion of smoking data for 730 subjects with such information 'did not confound by 10 percent or greater the relation between cumulative lung dose and lung cancer', but give no details.

Combined analysis of Mayak and Sellafield Plutonium Workers (European Union SOLO project)

(154) The EU SOLO project conducted a joint analysis of the Sellafield and Mayak cohorts. Analyses in terms of both lung cancer mortality and incidence demonstrated a clear effect of exposure to alpha-particles emitted by plutonium on both outcomes with the incidence ERR/Gy being somewhat higher than the mortality ERR/Gy. The pattern of the dose-response showed no indication of non-linearity or significant differences between cohorts, although the results were clearly dominated by the MWC data.

(155) Trends in background age-related rates of lung cancer morbidity and mortality were comparable between the Sellafield and Mayak cohorts, but a difference was observed in variation in background by year of birth or the calendar period. However, information about smoking status was not available in the framework of this analysis and the differing smoking habits in the UK and the Russian Federation may well explain these differences in birth cohort effects.

(156) The ERR associated with radiation dose, of both external gamma radiation and internal alpha-radiation from plutonium, was estimated taking into account all of the available non-radiation factors: those affecting background rates were cohort (i.e. MWC and SWC), sex, attained age and birth cohort, while those affecting the radiation risk estimates were sex and attained age. The pooled radiation risk analysis, in terms of the cumulative internal alpha-radiation dose to the lung from plutonium, revealed compatible ERR/Gy estimates to those obtained for the two cohorts separately.

(157) Examination of the plutonium dose-response for lung cancer incidence found significantly increased risks at relatively low doses for the SWC, 2-5 and 5-10 mGy using Mayak lung solubility assumption ($s_s = 2.5 \times 10^{-4}$ d^{-1}), and 1-2, 10-20 and ≥20 mGy using

Sellafield lung solubility assumption (s_s = 2.2 × 10^{-3} d^{-1}). In the MWC, an increased risk was only observed at relatively high doses (200-500 mGy using s_s = 2.5 × 10^{-4} d^{-1} and 50-100 mGy using s_s = 2.2 × 10^{-3} d^{-1}). As in previous MWC studies the plutonium dose-response was found to be linear across the whole dose range and the ERR/Gy point estimates were found to be consistent down to relatively low doses when restricting the range of plutonium dose included in the analysis. For example, in the incidence analysis a significant pooled ERR/Gy estimate was detectable at relatively low levels, 0.2 Gy when using s_s = 2.5 × 10^{-4} d^{-1} and 0.1 Gy when using s_s = 2.2 x 10^{-3} d^{-1}, with the ERR/Gy point estimates down to 0.05 Gy positive and consistent with the overall estimate.

(158) Study of potential effect modifiers on the plutonium ERR/Gy such as, attained age, sex and age at first plutonium exposure, was hampered by the lack of power in the SWC. For MWC, and, as a consequence, for the pooled cohort, it was found that sex and attained age were significant factors affecting the value of the ERR/Gy estimate. Sex significantly modified the plutonium ERR/Gy estimate in the MWC with Mayak females having a risk 4 times higher than Mayak males for incidence and 2-3 times higher for mortality. The SWC male ERR/Gy estimate was compatible with that of the MWC males but the number of female lung cancers was very low (10 deaths, 8 incidences) in the SWC and models that allowed the ERR/Gy estimate to vary by sex within the SWC converged poorly. In relation to attained age, a declining pattern in the plutonium ERR/Gy estimate with increasing attained age was observed in both cohorts, and although the power to detect this effect in the SWC was lower, the scale of this effect was very similar in both cohorts (e.g. for lung cancer incidence using s_s = 2.2 × 10^{-3} d^{-1} the age effect was Exp(-3.04 × log(age/60)) for MWC and Exp(-5.85 × log(age/60)) for the SWC).

European combined analysis of Plutonium Workers (European Union Alpha-Risk project)

(159) Grellier et al. (2017) obtained a lung cancer mortality Excess Odds Ratio (EOR) per Gy of lung dose from plutonium for the BNFL workforce (median lung dose in 232 controls, 0.85 mGy) of 48.8 (90% CI: <0, 195); these BNFL workers received their plutonium exposures at Sellafield. In comparison, in the SOLO project, Gillies et al. (2017) reported a lung cancer mortality ERR/Gy for Sellafield workers at an attained age of 60 years, using the s_s = 2.2 × 10^{-3} d^{-1} solubility assumption, of 20.6 (90% CI: <-1.5, 58.6). The ERR/Gy point estimates for the Sellafield workforce obtained from the SOLO and Alpha-Risk studies differ by a factor of greater than two, although it should be noted that lung doses will have been estimated on the basis of different dosimetry systems. These estimates are statistically compatible and also have wide confidence intervals that include 0 (i.e. are consistent with no excess risk).

(160) Grellier et al. (2017) found a lung cancer mortality EOR/Gy of lung dose from plutonium for all workers included in the Alpha-Risk study (median lung dose in 463 controls, 1.25 mGy) of 49 (90% CI: 16, 106). There was little variation in the EOR/Gy estimates when each contributing cohort was removed from the analysis: when the BNFL workforce was excluded the EOR/Gy becomes 50 (90% CI: 15, 117), and the lowest EOR/Gy estimate was obtained when the AWE cohort (median lung dose in 133 controls, 6.06 mGy) was removed to give 37 (90% CI: 0.18, 121).

(161) An unusual finding of Grellier et al. (2017) was that the lung cancer mortality associated with external dose for the BNFL workforce (median dose in 960 controls, 38.84 mGy) was borderline significantly negative, with EOR/Gy = -0.46 (90% CI: <0, 0.16). This compares with the equivalent external exposure ERR/Gy for the Sellafield workforce (all attained ages), obtained by Gillies et al. (2017) in the SOLO project using the s_s = 2.2 × 10^{-3} d^{-}

[1] solubility assumption (median external dose, 16.2 mGy), of 0.18 (90% CI: -0.27, 0.78). For all workers included in the Alpha-Risk study, the estimated lung cancer risk associated with gamma radiation dose (median dose in 1264 controls, 33.86 mGy) was EOR/Gy = -0.44 (90% CI: -0.6, 0.04), which contrasts with the strong positive association estimated with the plutonium alpha-particle lung dose: EOR/Gy 49 (90% CI: 16, 106) (median lung absorbed dose of 1.27 mGy) (Grellier et al., 2017).

Leukaemia, lymphatic and haematopoietic cancers

(162) For Sellafield, Omar et al. (1999) and McGeoghegan et al. (2003) both found that the plutonium workers had fewer deaths from, and incident cases of, leukaemia than expected compared to the national population, although Gillies and Haylock (2014) found that the rates of leukaemia deaths or cases were about the same as those of the national population. With a two-year lag, Omar et al. (1999) found no significant dose-response relationship between non-CLL leukaemia mortality or incidence and total (external plus plutonium) red bone marrow (RBM) dose, which averaged 51 mSv for plutonium workers. Among women, McGeoghegan et al. (2003) also failed to find a dose-response relationship for leukaemia risk with an average cumulative external dose of 23.3 mSv and an assessed internal lung dose of 3.45 mSv (taken as a surrogate for RBM dose from plutonium, which was not given).

(163) Only one significant result was reported, that for combined lymphatic and haematopoietic cancers. Contrary to what they found for leukaemia, Omar et al. (1999) found a significant trend with cumulative plutonium plus external radiation dose for incidence of all lymphatic and haematopoietic cancers among plutonium workers using a lag of 0, 10 or 20 years. Omar et al. (1999) reported that the association was also present for plutonium dose alone, the positive trend being due largely to two cases with cumulative plutonium doses >400mSv, cases of Hodgkin lymphoma and multiple myeloma.

(164) Leukaemia mortality and incidence in the Sellafield workforce was also a subject of study in the EU SOLO project examining the combined Mayak and Sellafield cohorts. However, the leukaemia component of the SOLO study has yet to be reported.

(165) In the USA, in their case-control study of non-CLL leukaemia, Schubauer-Berigan et al. (2007) found a positive relationship between leukaemia risk and total dose to the red bone marrow (ERR=4.0 per Sv, 95%CI -1.0-9.4), but it was not statistically significant. The average cumulative RBM dose of 30.6 mSv among cases was only slightly higher than that of 24.9 mSv among controls.

(166) The component of the EU Alpha-Risk case-control study that examined leukaemia mortality has yet to be published.

Liver cancer

(167) Other studies (apart from the Mayak studies) have reported results related to liver cancer. Among 5203 Sellafield plutonium workers employed during 1947-1975 and followed up to 1992, Omar et al. (1999) found one death from liver and gallbladder cancer when 5.08 deaths were expected from national rates (SMR=0.19, $p<0.01$). No incident cases (during 1971-1986) were reported while 3.13 were expected. In a later study, Gillies and Haylock (2014) found 15 deaths from, and 30 cases of, liver and gallbladder cancer among 12,272 plutonium workers employed at Sellafield during 1947-2002 and followed up to 2005, generating a non-significantly raised SMR of 102 and a SIR of 108. The ratio of the SMR with respect to that

for workers monitored for exposure to external sources of radiation only was significantly raised ($p<0.05$) at 2.49, but the ratio of SIRs was non-significantly increased at 1.81.

(168) In the USA, Wiggs et al. (1994) found 15 liver cancer deaths among 15,727 white male workers employed at Los Alamos, which was below the number expected from national rates, and none of these deaths occurred among 303 highly exposed plutonium workers. Of 5413 white male workers at Rocky Flats, 3 deaths from liver and gallbladder cancer were found (a non-significantly raised SMR of 139), but none of these deaths occurred among plutonium workers with estimated cumulative systemic depositions (lagged by 10 years) of ≥74 Bq (Wilkinson et al., 1987).

Bone cancer

(169) Omar et al. (1999), McGeoghegan et al. (2003) and Gillies and Haylock (2014) reported results for bone cancer and found no deaths among Sellafield plutonium workers. Omar et al. (1999) and McGeoghegan et al. (2003) found no incident case of bone cancer, and Gillies and Haylock (2014) reported 2 cases. Because this is a relatively rare cancer, in effect no deaths or cases were expected among the women included in the study McGeoghegan et al. (2003), and only 1.1 deaths and less than one incident case were expected among the Sellafield workers included in the study of Omar et al. (1999). The 2 incident cases included in the study of Gillies and Haylock (2014) gave a SIR of 94.

(170) In the USA, Voelz et al. (1997) reported a single death from bone cancer among 26 white men who had been highly exposed to plutonium during the Manhattan Project at Los Alamos. However, the number of deaths expected from national rates among such a small number of men was very small, so that even one death represented a highly statistically significant excess ($p<0.01$). The cumulative dose to the bone surface from plutonium for this man was calculated to be 0.44 Gy. Wiggs et al. (1994) reported that this death was the only one before 1991 among 303 highly exposed plutonium workers from Los Alamos. Wilkinson et al. (1987) found no death from bone cancer in 5413 white male workers at Rocky Flats.

Cancers at other sites

(171) Apart from lung cancer, the only other noteworthy result for respiratory cancers was reported for pleural cancer. Among British UKAEA workers monitored for plutonium, the SMR for pleural cancer when exposure was lagged by 10 years was 392 (95%CI 106-768) and the mortality rate was significantly higher than for other radiation workers (RR=6.7; 95% CI: 1.5, 28.5), but there was a (non-significant) negative trend with external radiation dose (Atkinson et al., 2004). Omar et al. (1999) found a statistically significant SMR of 471 ($p<0.001$; O=8, E=1.70) for plutonium workers at Sellafield, but the rate ratio when this SMR was compared to the significantly ($p<0.05$) raised SMR of 390 for other radiation workers at Sellafield was a non-significant RR=1.15; no dose-response was found for pleural cancer mortality and cumulative plutonium dose combined with external radiation exposure. The average dose to soft tissue for plutonium workers was 1.7 mSv. Given the strong association between pleural cancer and exposure to asbestos, it seems likely that the raised SMRs are due to asbestos exposure rather than to plutonium exposure (Omar et al., 1999; Atkinson et al., 2004).

(172) Among the UKAEA workers, Atkinson et al. (2004) reported an increased SMR for uterine cancer among female workers monitored for plutonium (SMR=669, 95%CI 134-1955). Restricting the uterine cancers to those of the endometrium increased the SMR to 1538 (95%CI

173-5555) and the RR=56.6 (95%CI 8.3-infinity) when compared to other radiation workers; the number of deaths was 3 and 2, respectively. There was a (non-significant) negative trend with external dose.

(173) For all Sellafield workers, Omar et al. (1999) reported a negative trend of all cancer mortality with cumulative plutonium effective dose plus external radiation dose assuming W class for plutonium. They found an elevated SMR of 144 ($p<0.05$) compared to the general population and an RR of 1.90 ($p<0.05$) among plutonium workers compared to other radiation workers for mortality from ill-defined and secondary cancers; no dose-response relationship was found for cumulative combined plutonium and external dose. Omar et al. (1999) reported a significant positive association between pancreatic cancer incidence and cumulative plutonium dose alone when the dose was lagged 10 years. Among female Sellafield workers, McGeoghegan et al. (2003) found a statistically significant increased rate ratio for mortality from all cancers in plutonium workers compared to other radiation workers. With the SMR for plutonium workers only slightly, and non-significantly, elevated (SMR=113), they attributed this excess to a deficit of cancers among the other radiation workers (SMR=51). Neither the SRR for all cancer incidence nor the RR when compared with the SRR for other radiation workers differed significantly from the null. No significant dose response was found with either cumulative plutonium dose or external radiation dose.

(174) An increase in breast cancer among Sellafield workers was reported by both Omar et al. (1999) and McGeoghegan et al. (2003). Omar et al. (1999) found a statistically significant increase for mortality for plutonium workers based on 6 deaths, with the SMR=236 ($p<0.05$) compared to the general population and RR=7.66 ($p<0.01$) compared to other radiation workers. This elevated RR was driven by a deficit of breast cancer deaths among radiation workers (SMR=34, O=2, E=5.92, $p<0.05$). Mortality risk among plutonium workers did not vary significantly with cumulative plutonium dose to soft tissues plus external radiation dose. No significant excess was found for cancer incidence (SRR=121, O=4, E=3.32). In the study of McGeoghegan et al. (2003) of female Sellafield workers, similar results were found: the SMR was 197 (O=7, E=3.50) among plutonium workers while the RR decreased to 3.77 ($p<0.05$) but remained statistically significant. As in the study of Omar et al., there was a deficit of breast cancer deaths among the other radiation workers (SMR=54, O=5, E=9.3). For incidence, the SRR was 144 (O=10, E=6.9) and the RR was 3.34 ($p=0.013$), which again was driven by a deficit of incident cases among other radiation workers (SRR=69, O=12, E=17.3); no dose-response was seen with cumulative plutonium dose. McGeoghegan et al. (2003) noted that for one of the breast cancer deaths included in the study of Omar et al. (1999) as occurring in a plutonium worker, urine samples were only taken after the diagnosis (and were found to be below the detection limit), and that if this death was excluded the SMR was no longer significantly elevated (O=5, E=1.15).

2.4. Calculation of lung cancer lifetime risk

2.4.1. Method of lifetime risk calculation

(175) Due to variations in the characteristics of the study populations (attained age, duration of follow-up), a direct comparison of ERR estimates obtained from different cohorts may be misleading. The calculation of the individual cumulated risk up to a given age in a specific exposure scenario can take into account such variations (Thomas et al., 1992). The cumulated risk, often called a lifetime excess risk, is obtained using:

- A risk model derived from a representative epidemiological study, with or without modifying factors (such as attained age, age at exposure or time since exposure). Use of such a model enables estimation of risk for other populations including extrapolations outside the range considered by the epidemiological study (exposure level, sex, duration of follow-up, attained age).
- Baseline reference rates for all-cause and lung cancer mortality or incidence. This allows calculation of the baseline lifetime risk of lung cancer in absence of exposure. Baseline rates are also part of the lifetime risk calculation when the risk model is expressed on a relative basis (i.e., ERR-based model).
- A scenario of exposure based on a given intake history.

(176) Lifetime excess risks can be estimated for either cancer incidence or mortality. We consider that the evidence reviewed in this report provides all elements needed to calculate lifetime risk of lung cancer mortality associated with plutonium exposure.

(177) For the purposes of illustration, the lifetime risk of lung cancer death associated with a scenario of exposure to plutonium was calculated for a male worker. The lifetime duration is taken to be 90 years, as is generally considered for workers by the Commission. The method used is the calculation of the Lifetime Attributable Risk (LAR) as described in NRC (2005) and Thomas (1992). The LAR is calculated using the survival function for a population unexposed to radiation, and is a close approximation to the more general risk of exposure-induced death (REID) which is calculated using a survival function that accounts for deaths due to the same exposure to radiation for which risk is estimated.

(178) Calculation of lifetime excess risk of lung cancer death was conducted by Sokolnikov et al. (2015b, 2017), using parameters presented by Gilbert et al. (2013), for a population of Russian males of working age (18 – 70 years) exposed to particularly high doses. We used here a similar approach, using updated dosimetric models and risk coefficients, based on unitary scenarios of plutonium exposure.

2.4.1.1. Risk models

(179) The most recent risk model derived from the cohort of Mayak workers was selected, quantifying the relationship between the radiation dose delivered to the lung due to plutonium intake and the ERR of lung cancer death. The model considers a linear relationship between dose and risk, with a strong decrease of this association (modifying effect) with increasing attained age. The model equation is:

$$ERR = \beta \cdot d \cdot e^{(\alpha \cdot ln(a/60))}$$

(180) for a cumulated lung dose d (in Gy) at attained age a (in years), β being the ERR per Gy and α being the coefficient reflecting the modifying effect of age.

(181) The model has been published by Gillies et al. (2017), and is based on plutonium lung dose estimated using the MWDS-2013 dosimetry system ($s_s = 2.5 \times 10^{-4}$ d^{-1}). In this model, the estimated ERR for males at attained age 60 years was 4.74 per Gy (90% CI 3.53; 6.24) with modifying effect of attained age α = -2.74 (95% confidence interval -4.51; -1.04). A 10-year lag time was considered between lung dose and lung cancer death.

(182) The variation of the ERR per Gy with attained age for the Gillies model is illustrated in Fig. 2.2 and compared with the ERR per Gy obtained using a previous model obtained from the Mayak cohort analyses published by Gilbert et al. (2013). The Gilbert model was based on plutonium lung dose (lagged by 5 years) estimated using the older dosimetry system (MWDS-

2008). In that model, the estimated ERR for males at attained age 60 years was 7.4 per Gy (95% CI 5 - 11), with modifying effect of attained age α = -3.1 (95% CI -5.4; -0.8).

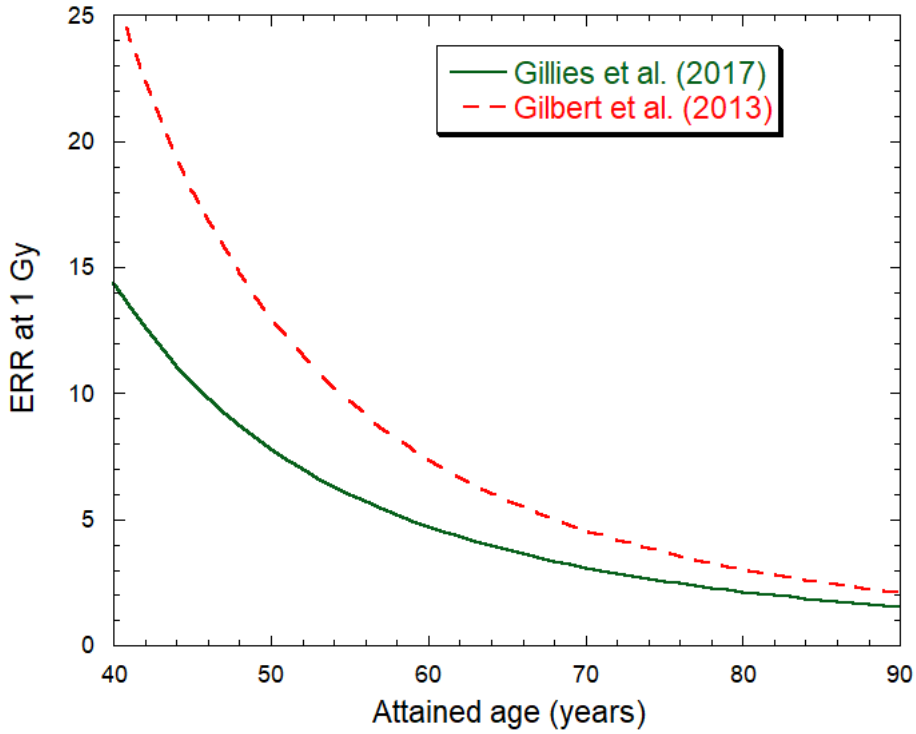

Fig. 2.2. Variation of the Excess Relative Risk coefficient per Gy of plutonium lung dose with attained age for males, according to (Gilbert et al., 2013) and to (Gillies et al., 2017).

2.4.1.2. Reference rates

(183) The reference baseline rates used are those provided in *Publication 103* (ICRP, 2007), for both general mortality and lung cancer mortality, for a Euro-American male population. We used Euro-American male reference mortality rates to be coherent with the risk models that were derived for Mayak workers. Fig. 2.3 shows the evolution of lung cancer baseline rates over age; rates increase sharply after age 40-44 (7.19 deaths per 100 000 per year) up to age 80-84 (464.57 per 100 000 per year) and decrease afterward. Based on these rates, the cumulated baseline risk from age 20 to 89 is 631 per 10,000 (Fig. 2.4).

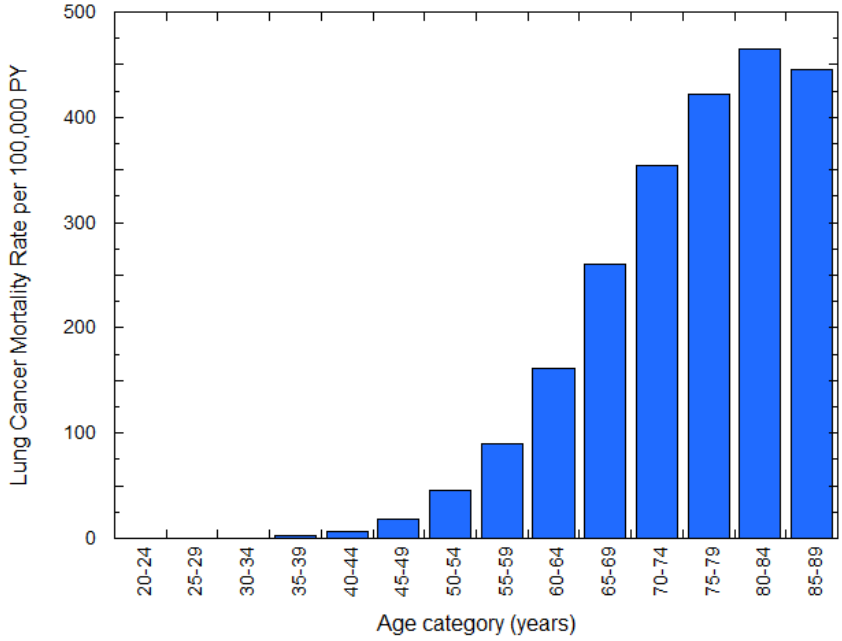

Fig. 2.3. Age-specific lung cancer mortality baseline rates for adult Euro-American males, according to (ICRP, 2007).

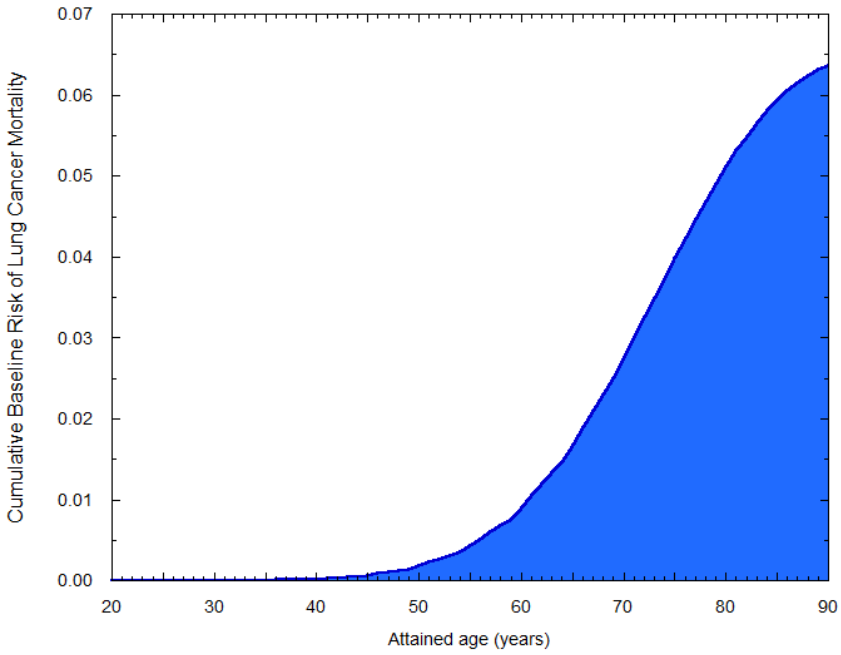

Fig. 2.4. Age-specific cumulative lung cancer mortality baseline risk, weighted by the probability of survival, for adult Euro-American males.

2.4.2. Unitary plutonium Intake Scenarios

(184) To allow comparison of estimated lifetime risk values among different exposure situations, we considered four exposure scenarios corresponding to a total intake of 1 Bq of ^{239}Pu as nitrate (moderately soluble) or oxide (relatively insoluble) forms, assuming either an acute intake or a chronic intake over 10 years. Plutonium intake was considered to occur at the

age of 20 years for the acute scenario and from age 20 years to 29 years for the chronic scenario. Annual absorbed doses to the lung were calculated from the time of intake up to the age of 89 years. These were calculated using *Publication 141* (OIR Part 4; ICRP, 2019) dosimetry. Characteristics of the scenarios are detailed in Table 2.7.

(185) These scenarios for unit intake provide a basis for the estimation of lung doses for different levels of exposure. For example, to calculate the dose for an acute intake of 1000 Bq at the age of 20 years, the cumulated dose given in Table 2.7 is multiplied by 1000.

(186) Figs. 2.5 and 2.6 present the distribution of annual lung dose over age for both acute and chronic plutonium intake, for plutonium nitrate or plutonium oxide, based on *Publication 141* (OIR Part 4; ICRP, 2019) dosimetry.

Table 2.7. Characteristics of plutonium exposure scenarios for a total intake of 1 Bq of ^{239}Pu assuming either an acute intake or a chronic intake over 10 years. The absorbed dose to the lung committed over 70 years (i.e. from ages 20 to 89 years) was calculated for plutonium nitrate or plutonium oxide based on *Publication 141* (OIR Part 4; ICRP, 2019).

	Age at intake (years)	Intake duration (years)	Intake rate (Bq/year)	Cumulated intake (Bq)	*Publication 141* (OIR Part 4) Lung dose* (μGy)
Acute intake					
Oxide	20	incidental	instantaneous	1	8.19
Nitrate	20	incidental	instantaneous	1	1.22
Chronic intake					
Oxide	20 – 29	10	0.1	1	7.85
Nitrate	20 – 29	10	0.1	1	1.19

*Total dose cumulated from age 20 to age 89 years (i.e. over 70 years)

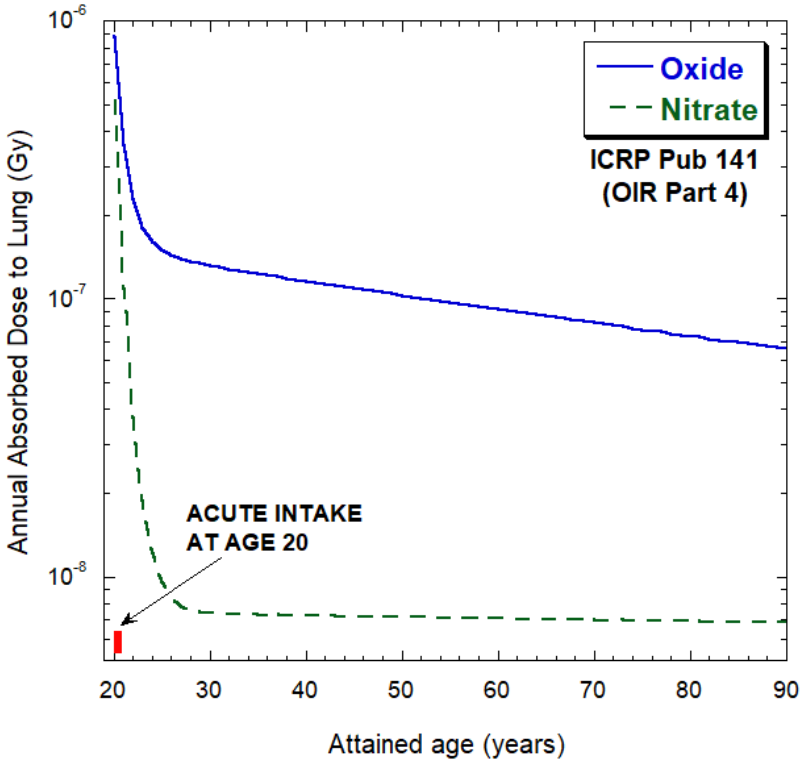

Fig. 2.5. Annual lung dose as a function of attained age for acute intake of 1 Bq of ^{239}Pu at age 20 years, for plutonium nitrate or plutonium oxide, calculated based on *Publication 141* (OIR Part 4; ICRP, 2019).

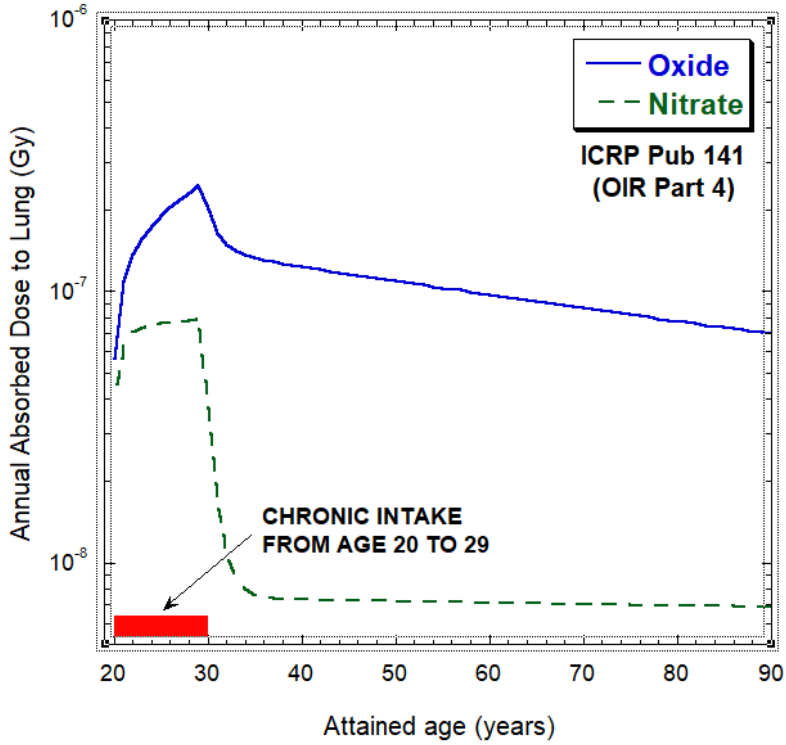

Fig. 2.6. Annual lung dose as a function of attained age for a total chronic intake of 1 Bq of ^{239}Pu, for plutonium nitrate or plutonium oxide, calculated based on *Publication 141* (OIR Part 4; ICRP, 2019). The exposure period is 10 years from age 20 to 29 years.

2.4.3. Results of lifetime risk estimates for unitary plutonium intake scenarios

(187) Lifetime risks of lung cancer mortality for each plutonium exposure scenario (acute vs chronic intakes and oxide vs nitrate) have been estimated using the most recent risk model derived from the epidemiologic studies of Mayak workers (Table 2.8), and based on lung doses derived using *Publication 141* (OIR Part 4) dosimetry.

(188) For a fixed total intake of 1 Bq, the cumulated doses to lung tissues from low solubility compounds (e.g. plutonium oxide) are higher than doses from compounds with higher solubility (e.g. plutonium nitrate). In the scenarios described in this section (Table 2.7), doses vary by more than a factor of 2 between the lower and higher solubility compounds.

(189) The lifetime risk estimates for the plutonium oxide and nitrates (Table 2.8) differ by a factor of 2 or less. The Gillies et al. (2017) risk model is linear with dose, but it also accounts for the dependency of risk on attained age. Since the lung doses vary with age (Figs. 2.5 and 2.6), differences between risks for different compounds do not entirely reflect the differences between total cumulated doses.

(190) It is concluded that it is now possible to estimate the lifetime risk of lung cancer attributable to plutonium exposure. Uncertainties associated with exposure reconstruction are very important, and different types of plutonium compounds can lead to very different cumulated doses (section 2.2.5). Reliable lifetime risk estimates can be achieved by good characterisation of the intake conditions (duration, timing, activity levels, and chemical form of compound).

Table 2.8. Lifetime risk of lung cancer mortality for scenarios with a total plutonium intake of 1 Bq, assuming either acute intake or chronic intake, of either plutonium nitrate or plutonium oxide, calculated based on *Publication 141* (OIR Part 4; ICRP, 2019) to calculate lung dose, and the risk model from Gillies et al. (2017).

	Baseline risk of lung cancer death * (deaths per 10,000)	Excess risk of lung cancer death (deaths per 10,000)	Excess risk of lung cancer death per Gy (deaths per 10,000)
Acute intake			
Oxide	631	0.012	1425
Nitrate	631	0.0021	1718
Chronic intake			
Oxide	631	0.011	1351
Nitrate	631	0.0020	1691

* Euro-American males (ICRP, 2007)

2.5. Discussion

2.5.1. Summary of risk estimation

(191) Strengths of the Mayak worker cohort include over 50 years of follow-up, reasonably complete mortality data, incidence data for residents of Ozyorsk, estimates of annual plutonium and external doses for individual workers, and a wide range of doses.

(192) An important limitation of the Mayak data is that despite extensive efforts by dosimetrists, plutonium dose estimates are subject to large uncertainties. As noted in section 2.3.1, for around two-thirds of the workers who had plutonium monitoring data and were included in the most recent analyses, plutonium dose estimates were based on only one or two bioassay measurements. Thus, plutonium doses are subject to large measurement errors, which are known to bias estimated risk coefficients toward zero if no adjustment is made. Additional sources of uncertainty in plutonium doses are discussed in section 2.3.5. It is hoped that in future, these uncertainties will be quantified in a way that allows them to be accounted for in dose-response analyses. Further, plutonium monitoring was only carried out for ~40% of workers who could have potentially been exposed to significant quantities of plutonium, so that surrogate measures of plutonium exposure have had to be developed for these workers.

(193) Most plutonium risk estimates were based on a mix of males and females and of smokers and non-smokers. Since most Mayak worker lung cancers occurred in male smokers, risk estimates for females and non-smokers are very imprecise, limiting the usefulness of the Mayak data for estimating risks in other populations. Even for estimating risks in male smokers, estimates may not be fully appropriate as smoking data for the Mayak cohort do not include data on rate (cigarettes per day) or duration of smoking.

(194) Despite these limitations, the Mayak worker cohort is unique in providing reasonably precise estimates of the plutonium dose-response for lung cancer and an opportunity to evaluate the dose-response for other types of cancers, particularly liver and bone cancers.

(195) Up to now, the results from studies of plutonium workers other than the Mayak cohort have not provided any consistent indication of an increased risk for the target organs/tissues of interest in respect of plutonium deposition, although the data are limited.

(196) The analysis of Sellafield workers by Gillies et al. (2017) demonstrated no consistent pattern of significantly raised risks by plutonium lung dose, although point estimates of lung cancer ERR were positive for all dose groups for both mortality and incidence for both lung solubility assumptions. The study of Grellier et al. (2017) found a significant positive association between lung dose from plutonium alpha-particles and lung cancer mortality.

2.5.2. Comparison of studies

(197) Patterns of risk in the Mayak cohort can be compared with those identified in underground hard-rock miners exposed to radon progeny (Marsh et al., 2014). For lung cancer, the magnitude of the decline in the ERR/Gy with attained age observed in Mayak workers was very similar to that based on eleven cohorts of underground miners analysed by the BEIR VI committee (NRC, 1999). In contrast to data on the eleven cohorts evaluated in BEIR VI and to more recent data from the Czech and French miner cohorts (Tomasek et al., 2008; ICRP, 2010a), there was no evidence of a decline in risk with time since exposure.

(198) Parallel analyses of data for Mayak workers and the Life Span Study (LSS) cohort of Japanese Atomic Bomb survivors who were aged 15-60 years at exposure were conducted by Gilbert et al. (2013). The Mayak worker risk estimates for plutonium exposure for males at age 60 years, expressed per Sv using a radiation weighting factor for alpha-particles of 20, was 0.35 (95% CI: 0.24 to 0.50), nearly identical to an estimate of 0.36 (95% CI: 0.04 to 0.78) based on LSS mortality data or an estimate of 0.34 (95% CI: 0.05 to 0.72) based on LSS incidence data. The ratios of female and male ERR estimates were also similar in the Mayak and LSS cohorts. However, confidence limits for LSS-based estimates were wide and compatible with much smaller or larger quality factors. The ERR in the LSS cohort, unlike that in the Mayak worker cohort, did not show a decline with attained age. The above comparisons of Mayak and LSS ERRs were based on analyses that included an attained age parameter that was intermediate between estimates for the Mayak and LSS cohorts.

(199) For lung cancer mortality at an attained age of 60 years in the male Mayak workforce, the ERR/Gy of lung dose from plutonium using the $s_s = 2.5 \times 10^{-4}$ d^{-1} solubility assumption was 4.74 (90% CI: 3.53, 6.24) (Gillies et al., 2017). This compares with the equivalent ERR/Gy estimate obtained by Gilbert et al. (2013) of 7.4 (90% CI: 5.0, 11), although it should be noted that Gilbert et al. (2013) lagged doses by 5 years whereas Gillies et al. (2017) lagged doses by 10 years, and that the lung dose estimates used by Gillies et al. (2017) were based on an updated dosimetry system.

(200) For lung cancer incidence at an attained age of 60 years in the male Mayak workforce, the ERR/Gy of lung dose from plutonium using the $s_s = 2.5 \times 10^{-4}$ d^{-1} solubility assumption was 5.27 (90% CI: 3.83, 7.12) (Gillies et al., 2017). This compares with the equivalent ERR/Gy estimates obtained by Labutina et al. (2013) of 7.1 (95% CI: 4.5, 10.9), although the lung dose estimates used by Gillies et al. (2017) relative to those of Labutina et al. (2013) were based on an updated dosimetry system.

(201) The final estimates for lung cancer risk associated with plutonium lung dose derived from the pooled MWC and SWC cohort analysis of Gillies et al. (2017) were within the range ERR = 5-8 per Gy for males at age 60 years for both mortality and incidence and using both lung solubility assumptions. These risk estimates are very similar in magnitude to those obtained in previous studies of the Mayak workers.

(202) Further, the lung cancer ERR/Gy estimated from the pooled MWC and SWC cohort in relation to external gamma-radiation were in the range 0.2-0.4 per Gy of gamma dose to the lung, which is similar to the results of past investigations of Mayak and Sellafield workers, and of other groups of persons exposed to low LET radiation.

2.5.3. Advantages and limitations

(203) The lack of consistency of results across studies is not surprising given the relatively small number of workers identified as plutonium workers in each study. With an average length of follow up in excess of 20 years for the cohort studies, there is adequate latency to identify cancers related to occupational exposure, but the small number of workers identified as plutonium workers coupled with the relatively low percentage of the cohort deceased diminishes the power of the studies.

(204) The different studies used standard methods for analysis. Several considered only mortality data (Brown et al., 2004; Wing and Richardson, 2005; Grellier et al., 2017), but others also considered incidence (Omar et al., 1999; McGeoghegan et al., 2003).

(205) Several studies did not provide estimates of dose-risk relationship for plutonium organ/tissue doses (Omar et al., 1999; McGeoghegan et al., 2003; Wing et al., 2004). Omar et al. (1999) and McGeoghegan et al. (2003) calculated organ/tissue dose estimates based on monitoring for plutonium with and without inclusion of external radiation exposure, but did not present any risk estimates based on these plutonium dose estimates. Instead, results from the analysis of trends with plutonium dose combined with external dose were presented. The remaining studies by Wing et al. (2000, 2004) and Atkinson et al. (2004) stratified the worker cohort based on the presence or absence of monitoring for plutonium exposure. Most of these studies estimated risks for plutonium workers in terms of external radiation doses, although the relevance of these estimates with respect to plutonium exposures is questionable given the noteworthy differences in the data and methods used to determine external radiation exposure.

(206) The estimates of ERR/Gy, for both external and internal plutonium exposure, obtained by Gillies et al. (2017) in the pooled MWC and SWC cohort show comparability of risks between those cohorts which suggests that the pooling of cohorts is acceptable, leads to increased statistical power and allows the study of a wider range of doses.

(207) To date the only firm evidence of cancer risks in relation to plutonium exposure has been based on findings from studies of the MWC. However, the scale of the exposures and the different dose assessment methodology used in the MWC mean that there is considerable uncertainty about whether the risks derived from this cohort could be extrapolated to low doses and are applicable to other cohorts. The SWC represents one of the few available companion cohorts with individual plutonium monitoring data available over a long period: around 500,000 urine sample results available for over 12,000 plutonium monitored workers covering the low dose range. The MWC and SWC therefore represent complimentary resources for studying the health effects associated with plutonium exposure. The combining of these cohorts within a unified dosimetry methodology has enabled the study of plutonium risks over a wider dose range than could be managed using the MWC alone.

(208) The results obtained in the pooled MWC and SWC cohort suggest that the estimated lung cancer risks are applicable to other cohorts, as comparable risks associated with plutonium exposure were found in the two contributing cohorts. However, at the present time the power to detect risks in the SWC is relatively low and hampered by the large uncertainty surrounding dose assessments based on early urine sample results. In the MWC, the power to detect effects is high across the mid to high dose range but the power to detect effects at low doses is

hampered by the relatively high limit of detection in place in MWC for a large proportion of follow-up. For the MWC the power to detect effects at low dose could potentially be improved by the addition of post-1982 workers into the cohort, or by the reconstruction of doses for those workers who were potentially exposed to high levels of plutonium but were not monitored. The power to detect effects in the SWC could be improved by extending follow-up, which would increase the data for the sub-cohort of Sellafield workers whose dose assessments are based on high quality sample results, and by efforts to improve the dose assessments for early Sellafield workers, and through the creation of a plutonium job-exposure matrix (Riddell et al., 2019; de Vocht et al., 2019).

2.5.4. Relative biological effectiveness of plutonium for lung cancer

(209) The relative biological effectiveness (RBE) of different types of ionising radiation, the ratio of the absorbed doses of two types of radiation that produce the same level of a specified effect as estimated largely from experimental studies on cells or animals, are the basis for the radiation weighting factors (w_R) recommended by the Commission (*Publication 103*) for the purposes of radiological protection. The recently published Mayak studies on risk from plutonium exposures, and the lifetime risk estimates presented in section 2.5, can be used to gauge the RBE of alpha-particles emitted by plutonium, in particular, and of alpha-particles, in general. For alpha particles, *Publication 103* recommends a radiation weighting factor (w_R) of 20 for the calculation of equivalent and effective doses for radiological protection purposes.

(210) The ERR/Gy values obtained by Gillies et al. (2017) in the pooled MWC and SWC cohort for both external and internal plutonium exposure allow an estimation of relative biological effectiveness (RBE) for alpha-particles emitted from plutonium and the resulting risk of lung cancer: the point estimate obtained from this investigation is within the range of 10-30, which can be considered, in view of uncertainties in both the estimation of risk itself and of dose measurements and estimation, as a broad confirmation of the appropriateness of the value currently adopted in radiological protection as the radiation weighting factor for alpha-particles of 20.

(211) In this section we investigate the biological effectiveness of plutonium alpha particles relative to high energy photons by comparing the lifetime risks of lung cancer mortality for plutonium exposures estimated using the Gillies et al. (2017) risk models from the Mayak workers (section 2.4.1) with lifetime risks of lung cancer mortality based on risk models derived from Life Span Studies (LSS) of the Japanese atomic bomb survivors. In this exercise, the reference radiation for comparing the health effects of plutonium is high-energy photons (i.e., alpha-particles relative to gamma-rays) and the health endpoint is lung cancer mortality. The biological effectiveness of alpha particles is estimated as the ratio of the lifetime risk from exposure to plutonium to the lifetime risk from an exposure to high energy photons described by annual absorbed doses to lung (Gy) identical to those estimated for each of the plutonium intake scenarios described in section 2.4.2.

(212) The lifetime risk from exposure to high-energy photons has been estimated using the risk model for lung cancer mortality for the LSS cohort reported by Ozasa et al. (2012). The LSS included 86,611 subjects with a follow-up period from a 1950–2003. Weighted doses to LSS cohort members were estimated using the DS02 dosimetric system, based on the gamma dose plus a small contribution from exposure to neutrons. The dose-response for lung cancer mortality has been derived using estimates of lung absorbed dose (in Gy), based on a total of 1558 lung cancer deaths.

(213) Excess relative (ERR) and excess absolute (EAR) rate models have been derived for lung cancer mortality in the LSS cohort. The models indicate a response linear in dose, adjusted by age and sex modifiers:

$$ERR\ or\ EAR = \beta d \cdot exp(\tau\, e^{*} + \upsilon\, ln(a^{*})) \cdot (1 + \sigma\, s)$$

(214) where d is dose, s is sex, $e^{*} = (e - 30)/10$ and e is age at exposure, $a^{*} = a/70$ and a is attained age, and σ, τ and ν are coefficients for effect modification (Table 2.9).

(215) For the ERR model, parameter β represents the sex-averaged ERR per unit dose (Gy) at attained age 70 years after an exposure at age 30 years. For the EAR model, parameter β represents the sex-averaged EAR per unit dose (per 10^4 person-year Gy) at attained age 70 years after an exposure at age 30 years.

Table 2.9. Parameter values and effect modifiers of the ERR and EAR models for lung cancer mortality from the LSS study (Ozasa et al., 2012)

Parameter		ERR Model*	EAR model*
Risk per unit dose	Sex-averaged (β) ERR/Gy or EAR/10^4 PY.Gy	0.75 (0.51, 1.03)	6.5 (4.3, 9.0)
Modifiers			
Sex	Female/Male ratio (σ)	2.7 (1.3, 6.8)	0.78 (0.40, 1.8)
Age at exposure	Percent change per 10-yr increment (τ)	–7% (-35%, 29%)	–16% (-37%, 6%)
Attained age	Exponent of attained age (ν)	–0.04 (-2.2, 2.6)	6.2 (4.5, 8.2)

*Best estimate and 95% confidence interval

(216) Lifetime attributable risks (Thomas et al., 1992; NRC, 2005) from exposures to high energy photons have been estimated based on the ERR and EAR models from Ozasa et al. (2012) separately by using (a) the lung doses corresponding to exposure scenarios described in section 2.5.2, (b) the baseline rates of lung cancer mortality and survival functions for *Publication 103* Euro-American male population, and (c) a 10-year lag representing the minimum latency period (as in the main analyses in Gillies et al. (2017)). Lifetime risks have been integrated from the beginning of exposure at age 20 years up to age 89 years.

(217) These lifetime risks obtained from the Japanese LSS were divided by a DDREF of 2, as recommended in *Publication 103*, for the application of risk models derived from a cohort acutely exposed to gamma rays to a chronic exposure situation relevant for a comparison with the plutonium intake scenarios described in section 2.5.2.

(218) Results of the lifetime risk calculation are presented in Table 2.10. The lung cancer mortality risks from exposures to alpha particles are larger than the risks from low-level exposure to high energy photons by a factor of about 15 to 22, depending on the exposure scenario and choice of model (ERR vs EAR).

Table 2.10. Comparison of lifetime lung cancer risks estimated for exposures to plutonium alpha particles and high energy photons assuming the same lung dose distribution. Lung dose distribution obtained for a total intake of 1 Bq of ^{239}Pu.

	Lifetime lung cancer risk[†] (deaths per 10,000)			Mayak alpha-particles (Gillies) divided[‡] by LSS Photons (ERR Model)	Mayak alpha-particles (Gillies) divided[‡] by LSS Photons (EAR Model)
	Pu Alpha-partcles Mayak	High Energy Photons LSS			
	Gillies et al ERR Model	Ozasa et al ERR Model[*]	Ozasa et al EAR Model[*]		
Acute intake					
Oxide	0.012	0.00074	0.00055	15.8	21.2
Nitrate	0.0021	0.00014	0.00011	15.5	19.3
Chronic intake					
Oxide	0.011	0.00066	0.00048	16.0	22.1
Nitrate	0.0020	0.00013	0.000098	15.8	20.5

[*] Reduced by a DDREF of 2

[†]Euro-American male

[‡]Reported values represent ratios lifetime risks before rounding to two digits (ratio of unrounded LAR estimates).

(219) The above results suggest a RBE of plutonium alpha particles relative to high-energy photons equal to about 15 to 16 when based on the ERR model and 19 to 22 when based on the EAR model. Note that without the application of a DDREF of 2 to the lifetime risk estimate derived from the LSS models, the estimated RBE would be a factor of two lower (indicating values of 7-11).

2.5.5. Comparison with the relative biological effectiveness of radon for lung cancer

(220) In *Publication 115* (ICRP, 2010a), a nominal risk coefficient of 5×10^{-4} per working level month (WLM, i.e. 1.4×10^{-4} per mJh m^{-3}) was adopted for the lung detriment per unit exposure to radon and its progeny, on the basis of a review of epidemiological studies of underground miners, including studies with relatively low levels of exposure. Risk models used for the calculation of lifetime risk were ERR models derived from miner studies, considering a modifying effect of exposure rate and time since exposure, and with a minimal lag time of 5 years between exposure and lung cancer death (ICRP, 2010a). Lung cancer baseline rates were reference rates averaged over males and females and over Euro-American and Asian populations of *Publication 103* (ICRP, 2007). The exposure scenario considered was a constant low-level exposure to 2 WLM per year during adulthood from 18 to 64 years of age, and the

risk was estimated up to 90 years of age. Repeating the calculation using only the baseline rates for Euro-American males instead of the reference rates averaged over males and females and over Euro-American and Asian populations gives a lifetime risk estimate of about 7×10^{-4} per WLM (ICRP, 2010a).

(221) A lung equivalent dose of 24.3 mSv per mJh m^{-3} (86 mSv per WLM) of exposure to radon progeny for male miners was calculated in *Publication 137* (ICRP, 2017), with a radiation weighting factor w_R of 20 for alpha particles (ICRP, 2007). This corresponds to a detriment-weighted absorbed dose to lung, as defined in section 2.2.2 para. (50), of 4.3 mGy per WLM.

(222) The scenario of radon exposure considered in *Publication 115* therefore corresponds to an absorbed dose rate to lung of 8.6 mGy per year from age 18 to 64 years, with a total exposure of 94 WLM corresponding to a total lung absorbed dose of 0.40 Gy. With the lifetime excess absolute risk value of 7×10^{-4} per WLM for Euro-American males (ICRP, 2010a) and a detriment-weighted absorbed dose to lung of 4.3 mGy per WLM (ICRP, 2017) gives a corresponding lifetime lung cancer risk per lung dose of 1628 deaths per 10^4 per Gy (i.e. 0.16 Gy^{-1}).

(223) For comparison, under the same scenario of exposure, a lifetime attributable risk, integrated up to age 90 years, was estimated from exposure to high energy photons, using the ERR model from Ozasa et al. (2012) presented in Table 2.7. The same estimate of annual absorbed doses to lung of 8.6 mGy per year from 18 to 64 years of age was used. Also, the baseline rates of lung cancer mortality and survival functions of *Publication 103* for Euro-American males were used, with a 5-year lag representing the minimum latency period, as in *Publication 115*. A DDREF of 2 was applied to derive the excess risk from the LSS ERR model, and an excess of 113 deaths per 10^4 per Gy (1.13×10^{-2} Gy^{-1}) was obtained.

Table 2.11. Comparison of lifetime excess risk per a lung dose of 1 Gy, from exposure to plutonium (4 exposure scenarios), radon and high energy photons for Euro-American males.

Exposure scenario	Plutonium (dose *Publication 141*)		Radon (dose *Publication 137*)	
Risk model	Mayak ERR (Gillies, 2017)	LSS ERR (Osaza, 2012) DDREF = 2	Miner ERR (*Publication 115*)	LSS ERR (Osaza, 2012) DDREF = 2
Lifetime excess risk of lung cancer death (deaths per 10^4) per lung dose (Gy)	1351-1691	85-107	1628	113
Ratio of lifetime excess risk of lung cancer death per Gy between internal and external exposure	15.5 – 16		14.4	

(224) Table 2.11 compares the lifetime excess risk of lung cancer death per unit lung dose for exposure to plutonium, radon progeny and high energy photons. The risk from exposure to alpha particles emitted by radon progeny is larger than the risk from exposure to high energy photons by a factor of about 14, which is consistent with the factor of about 15 to 16 between risks from exposure to plutonium and to photons (section 2.6.1). These figures would suggest a biological effectiveness for lung cancer mortality of alpha particles relative to photons equal to about 14 to 16.

2.5.6. Interpretation of the estimated Relative Biological Effectiveness values

(225) The RBE values estimated for plutonium and radon progeny are comparable with the radiation weighting factor (w_R) recommended by ICRP for alpha particles. While most inferences about the biological effectiveness of alpha particles have been based on studies of cancers in animals or studies of transformation in cells (NCRP, 1990; Muirhead et al., 1993), the results presented here are based on human epidemiological data.

(226) Nevertheless, care has to be taken in makingsuch comparison, as the w_R is intended to embrace all cancer risks whereas only lung cancer mortality is considered in the present calculations, and plutonium related risks have been observed for liver and bone (section 2.4.1) for which different RBEs for alpha radiation may apply.

(227) Also, important uncertainties are associated with the derived biological effectiveness, including statistical uncertainties in the parameter values of the risk models, uncertainties related to dosimetry, uncertainties related to the transfer of risk (ERR vs. EAR risk models) and DDREF, and uncertainties related to the effects of smoking (section 2.5.3). For example, applying the LSS EAR model to the miner scenario of exposure would yield a lower estimate of 80 deaths per 10^4 per Gy (instead of 85-107, Table 2.9). In the same way, considering a lag time of 10 years (instead of 5 years) would have led to slightly lower values. The choice of the energy for the reference photon radiation, either x rays or high energy gamma rays, is another factor possibly influencing any estimation of RBE.

(228) Therefore, it should be kept in mind that the value of RBE estimated here for alpha particles emitted by plutonium and radon progeny concerns only the risk of fatal lung cancer, and correspond to specific scenarios of exposure, while the w_R is a judgement value for radiological protection purposes and applies to all stochastic effects of alpha radiation, including other types of cancer. Finally, the contribution to effective dose of lung dose from internal emitters of alpha particles is directly proportional to the value assigned to the tissue weighting factor w_T for lung.

2.5.7. Potential impact of uncertainties

(229) As discussed in section 2.2.5, uncertainties associated with internal dose assessments based on bioassay data can be quite large. Nevertheless, epidemiological studies that evaluate site-specific cancers from occupational exposure to plutonium have generally not considered the uncertainties in the dose assessment. At best, the impact of these uncertainties has only been discussed qualitatively. Generally, only point estimates of doses are available without any estimate of uncertainty.

(230) In addition to dose uncertainties, other limitations can exist that are related to the epidemiological design (selection bias, lost to follow-up, statistical power, confounding) and to the modelling of the relationship between radiation exposure and risk (shape of the dose-risk relationship, modifiers of the dose-risk relationship) (UNSCEAR, 2018).

(231) The MDWS 2013 system and the Gillies et al. (2017) risk model apply for a mixed population of both smokers and never smokers. The risks of lung cancer deaths have been estimated for the Euro-American male population which also represents a population that includes both smokers and never smokers. However, the prevalence of smoking could be different in the Mayak cohort and in the Euro-American male population for which the risks were estimated.

(232) Calculations of the distribution of annual lung doses over age for the given exposure scenarios presented in section 2.5.2 have also been performed using the MWDS-2013 instead of *Publication 141* for the lifetime lung cancer mortality risk calculations. Using MWDS-2013, lung doses would have been about 25% lower for oxide and about a factor of two higher for nitrate than doses presented in Table 2.5. The impact of the dosimetry system on lifetime risks per unit intake would have been similar to the impact on the magnitude of doses, with lifetime risks being 20% lower for oxide and about twice as high for nitrate if using MWDS-2013 (compared to results presented in Table 2.6). However, the lifetime risks per Gy for both dosimetry systems are similar with values of 0.15 to 0.19 Gy^{-1} for the MWDS-2013 and values of 0.14 to 0.17 Gy^{-1} for the OIR Part 4 dosimetry. Likewise, the ratio of lung cancer mortality risk between exposures to plutonium alpha particles and exposure to high energy photons using ERR models would have also been about 16 using the MWDS-2013 (similar to the range of 15 to 16 using *Publication 141* (OIR Part 4), as presented in Table 2.8). These results indicate that the choice of dosimetry system used to calculate the distribution of annual lung doses over age for the given exposure scenarios is not a very sensitive factor in the calculations of the lifetime lung cancer risk per Gy. However, the dosimetry system used to calculate the Mayak worker doses for the epidemiological analysis is an important factor.

(233) The absorbed dose to each target region of the lung is calculated separately. The lung dose (or the 'detriment-weighted absorbed dose' to the lung) considered in Table 2.7 is the arithmetic mean of the absorbed doses to the BB, bb and AI regions of the lung, consistently with the equal apportionment of the detriment applied in *Publication 130* (ICRP, 2015) for calculation of the equivalent dose to lung. However, apportionment factor (A_{BB}:A_{bb}:A_{AI}) values of ~(0.6:0.30:0.1) are consistent with regional distribution of lung cancer types in the general population of smokers and non-smokers [*para*. (92)]. Assuming these values instead of the Commission's default values (⅓: ⅓: ⅓) decreases the detriment-weighted absorbed dose to the lung per unit intake by about 1.5 and 2.2 for plutonium nitrates and oxides respectively [*para*. (94)]. It is difficult to infer the effect of different apportionment factors on the lifetime risk per Gy estimates without repeating the dosimetric calculations and the epidemiological analysis itself. However, it is likely that the lifetime risk per Gy estimates would be about a factor of 1.5 to 2 greater with apportionment factors of ~ (0.6:0.30:0.1). Correspondingly, the estimated RBE would be about 1.5 to 2 greater.

(234) The lifetime lung cancer risk of death was also calculated for the Euro-American male population based on exposure to radon progeny (Section 2.5.5). Assuming apportionment factor (A_{BB}:A_{bb}:A_{AI}) values of ~(0.6:0.30:0.1) instead of the Commission's default values (⅓: ⅓: ⅓) increases the detriment-weighted absorbed dose to the lung per unit exposure by about a factor of 1.2 (ICRP, 2017). Consequently, the lifetime lung cancer risk per Gy estimate and the estimated RBE based on radon progeny exposure would be about 1.2 lower with apportionment factors of ~(0.6:0.30:0.1).

(235) The comparison of risk per lung dose between protracted irradiation by alpha particles from plutonium or radon progeny and acute exposure at moderate-to-high gamma-ray doses in the LSS cohort is performed with the application of a DDREF to the LSS risk estimates. As a

ratio of these risks, the value of RBE estimated here for alpha irradiation of the lung is proportional to the assumed value of DDREF, because the radiation weighting factor is based on RBE values with respect to low-level gamma-ray exposures. A value of 2 is used by the Commission to derive risk coefficients for all types of solid cancer. The choice of a DDREF of 2 by the Commission is based upon dose-response features of experimental data and upon the epidemiological data of the LSS available in the 1990's (ICRP, 1991). Its magnitude is uncertain as highlighted by different analyses (NAS/NRC, 2006; Kocher et al., 2005, 2018, 2019; Wakeford et al., 2019) and this uncertainty propagates to that of the present RBE estimation for plutonium alpha particles and lung cancer mortality. A reappraisal of the validity of the DDREF regarding current scientific knowledge is ongoing in the frame of aTask Group of the Commission (Rühm et al., 2015, 2016, 2018; Shore et al., 2017; Tran and Little, 2017). Applying no DDREF to the lifetime risks derived from the LSS ERR model would suggest a RBE value of about 7-8 instead of 14-16.

3. CANCER RISK FROM EXPOSURE TO URANIUM

3.1. Introduction

(236) Given the weak evidence for the risk of cancer consequent to ingestion of uranium, the quantitative evaluation of uranium carcinogenicity undertaken in this section is limited to occupational exposure to uranium resulting from the processing of the uranium ore through milling and refining, chemical conversion, enrichment, fuel fabrication, and reprocessing. Although increased lung cancer risk has been found among underground uranium miners, this excess has been attributed to inhalation of radon and its decay products emitted by the ore, and exposure of the lung to radon progeny. The relationship between radon and its progeny and lung cancer is discussed in *Publication 115* (ICRP, 2010a) and is not considered in detail in this report.

(237) The likelihood of internal radiation exposure from occupational intakes of uranium varies throughout the nuclear fuel cycle and is dependent upon the processes, the techniques used and the chemical characteristics of uranium exposure. Subsequent to the mining of raw uranium ore, milling consists of crushing and grinding ore followed by chemical leaching, separation of uranium from the leachate, and precipitation as 'yellowcake' – a chemically complex mixture of diuranates, basic uranyl sulphate, and hydrated uranium oxides – which contains 70-90% uranium. During uranium conversion, U_3O_8, the main component of the yellowcake, is reduced to UO_2 using hydrogen, then to UF_4 by addition of hydrofluoric acid, and finally to UF_6 by exposure to fluorine. Gaseous diffusion or gas centrifuge plants may be used to enrich the ^{235}U in the uranium in UF_6 for commercial purposes from 0.72% ^{235}U to about 3-5% ^{235}U, and to higher enrichments for research and military purposes. After enrichment, UF_6 is reconverted into metallic uranium or UO_2 for fuel fabrication. Fuel reprocessing involves dissolution of the irradiated fuel elements in acid, followed by chemical separation of uranium and plutonium from the solution.

(238) In 2012, the International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence of the carcinogenicity of uranium from studies using experimental animals, but that evidence was limited in humans exposed to mixtures of natural, enriched and depleted uranium (IARC, 2012). Recently, in its 2016 Report, UNSCEAR (2017) published an extensive review focusing on biological effects of uranium in experimental studies of laboratory animals, and in epidemiological studies of workers and the general population.

(239) The present publication provides a critical summary of the UNSCEAR Report 2016 (2017) and discusses the impact of recent epidemiological studies. In contrast to the UNSCEAR Report 2016 (2017), the focus here is on studies of uranium workers with predominant exposure to uranium, thus excluding studies of uranium miners primarily exposed to radon and its progeny.

3.2. Dosimetric and toxicological aspects

(240) Because of variations in the type and size of airborne uranium particles and the chemical form of uranium contained in particles, the solubility and resulting biokinetic distribution of uranium in the human body differ significantly (ICRP, 2017). Inhalation of soluble uranium compounds leads to ready absorption from lungs to blood, leading to organ retention and principally urinary excretion. Insoluble uranium, however, is retained in the lungs

to a larger extent, with a greater proportion being transported to tracheobronchial or other thoracic lymph nodes, or escalated from the lungs and swallowed. Consequently, health hazards are likely to vary across the nuclear fuel cycle because of the different forms of uranium present in each stage (Ansoborlo et al., 2002).

(241) Depending on the chemical compound, uranium may display any reference absorption type from the respiratory tract (F, M, S) and about 0.2 to 2 percent is absorbed from the small intestine (ICRP, 2017).

(242) The ICRP biokinetic and dosimetric models applicable to uranium, and material specific absorption parameter values, are presented in *Publication 137* (ICRP, 2017). To estimate internal uranium exposure in a cohort of US enrichment workers, Anderson et al. (2013) implemented the former models of *Publications 66* (ICRP, 1994a) and *69* (ICRP, 1995) in the InDEP computer code. Intakes were evaluated from bioassay data using either a least-square method or a Bayesian method. Uncertainties on biokinetic models, dose coefficients and bioassay data were quantified by lognormal probability distributions based on literature and expert judgment, and propagated by Monte Carlo calculation.

(243) As a heavy metal, uranium displays chemical toxicity in addition to delivery of radiation dose. The main target organ to be considered for uranium toxicity is the kidney (WHO, 2001; ATSDR, 2013).

(244) Uranium hexafluoride induces irritation at high doses; some uranium compounds may cause pulmonary effects at relatively high inhalation exposures. However, long-term exposure to lower concentrations (generally less than 10 mg m^{-3}) has usually not resulted in pulmonary toxicity. No consistent or confirmed adverse chemical effects of uranium have been reported on skeleton or liver. Effects of chronic ingestion of uranium in drinking water on bone metabolism were studied among 146 men and 142 women 26-83 years of age who for an average of 13 years had used drinking water originating from wells drilled in bedrock, in areas with naturally high uranium content (Kurttio et al., 2005). There was some suggestion that elevation of CTx, a marker for bone resorption ($p = 0.05$) as well as osteocalcin, indicator of bone formation ($p = 0.19$) could be associated with increased uranium exposure (uranium in water and intakes) in men, but no similar relationship was found in women. No reproductive or developmental effects have been reported in humans. Although uranium may accumulate in the central nervous system (CNS) tissue, and some animal and human studies are suggestive of effects on CNS function, it is difficult to draw firm conclusions from the few studies reported.

(245) In the kidney, proximal tubules are considered to be the main target. There is limited information from human studies indicating that the severity of effects on kidney function and the time taken for renal function to return to normal both increase with the level of uranium exposure. Currently, uranium is regarded as a less potent nephrotoxin than the classical nephrotoxic metals (cadmium, lead, mercury). A cohort of Gulf war I veterans exposed to depleted uranium was followed since 1994. They were divided in two groups: low exposure (urine uranium levels of <0.1 μg g^{-1} creatinine) and high exposure (urine uranium levels of ≥ 0.1 μg g^{-1} creatinine and usually bearing embedded DU fragments). No significant differences in parameters of kidney function were observed between the two groups and the values were in normal ranges. However, some parameter changes were close to statistical significance. Effects of chronic ingestion of uranium in drinking water on kidney function were studied in Canada (Limson Zamora et al., 1998) and in Finland (Kurttio et al., 2006a). In both studies, uranium intake was associated with increased glucose excretion in urine and the study in Finland also showed a small effect on blood pressure, however, no damage to glomerular function was observed. Renal effects have been observed in animals exposed to aerosols of

soluble uranium compounds at concentrations of at least 0.13 mg U m^{-3} for intermediate durations. However, no renal effects were observed in animals exposed to 1.1 mg U m^{-3} as insoluble compounds; the lowest-observed-adverse-effect level was 8.2 mg U m^{-3}.

(246) On the basis of animal experiments and human data, the US Agency for Toxic Substances and Disease Registry (ATSDR) calculated minimum risk levels (MRLs) for chemical toxicity of uranium under some situations of exposure. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (acute kidney damage) over a specified duration of exposure. MRLs of 0.002 mg U m^{-3} and 0.0008 mg U m^{-3} have been derived for intermediate-duration inhalation exposure (15– 364 days) to insoluble and soluble compounds of uranium respectively. MRLs of 0.0008 mg U m^{-3} and 0.00004 mg U m^{-3} have been derived for chronic-duration inhalation exposure (365 days or more) to insoluble and soluble compounds of uranium respectively. MRLs of 0.002 mg U kg^{-1} day^{-1} and 0.0002 mg U kg^{-1} day^{-1} have been derived for acute-duration (≤15 days) and intermediate-duration (15– 364 days), respectively, oral exposure to soluble compounds of uranium. The database was considered inadequate for derivation of a chronic-duration oral MRL (ATSDR, 2013).

(247) Leggett et al. (2012) reviewed the literature on chemical toxicity of uranium and applied ICRP (1994, 1995, 2006) biokinetic models to adopt a reference primary guidance for prevention of chemical toxicity from intake of uranium and concluded that the concentration of uranium in the kidneys should not exceed 1.0 μg uranium per g of kidney at any time.

(248) From available biological and health effects data, WHO has adopted a tolerable intake (TI) approach to derive a guideline value for the chemical toxicity of depleted uranium (DU). WHO (2001) concluded that limitation on public intake of soluble DU compounds (Type F and M) should be based on a TI value of 0.5 μg per kg of body weight per day, and for insoluble (Type-S) DU compounds on 5 μg per kg of body weight per day. The TI value of 0.5 μg per kg of body weight per day leads to a limitation on public inhalation of soluble DU compounds to 1 μg m^{-3} DU in air; the same guideline air concentration of 1 μg m^{-3} DU in air for insoluble DU compounds comes from the radiation limit dose of 1 mSv $year^{-1}$. The 8-hour time-weighted average limitation on worker inhalation of soluble and insoluble DU compounds is 50 μg m^{-3} DU in air.

(249) A report of the United Kingdom Royal Society assessed the health hazards associated with the use of DU munitions following the military conflicts in the Persian Gulf and the Balkans (Royal Society, 2001, 2002). Part II of the report considered the chemical toxicity effects of uranium on the kidney (Royal Society, 2002). Based on the limited human exposure data, it was reported that adverse effects can be detected at chronic intakes that result in kidney levels of 0.1- 0.5 μg uranium per g of kidney, or acute intakes resulting in about 0.5 μg per g of kidney. However, the long-term effects (if any) of these elevated uranium levels are not clear. These toxicity reference values were supported by a further review of the scientific literature including several human studies that were not considered by the Royal Society Working Group (Hodgson et al., 2007). It was also noted that for humans, the ratio of uranium urinary excretion to kidney concentration shows no obvious change up to kidney concentrations of at least 3 μg uranium per g of kidney (Hodgson et al., 2007).

(250) The Royal Society Working Group noted that the kidney is a resilient organ and that about two-thirds of kidney function can be impaired without obvious clinical signs of disease. It was also noted that normal kidney function can be restored even after a large acute intake of uranium, although some abnormalities may remain detectable for several years (Royal Society,

2002). The long-term effects of acute uranium poisoning in humans are not well known but there could be kidney failure in later life.

3.3. Epidemiological studies

3.3.1. Description of studies

(251) The relationship between internal uranium exposure and cancer in nuclear fuel cycle workers was the subject of several extensive literature reviews and meta-analyses (Guseva Canu, 2008; Zhivin et al., 2014; Stammler et al., 2016), and was also addressed in the recent UNSCEAR 2016 Report (UNSCEAR, 2017). Table 3.1 summarises these data and includes the seven most recent studies (Grellier et al., 2017; Yiin et al., 2017, 2018; Bouet et al., 2018, 2019; Zablotska et al., 2018; Golden et al., 2019) published after the completeion of the UNSCEAR 2016 Report (UNSCEAR, 2017). Studies are grouped by type of uranium work (e.g., uranium milling, uranium conversion) and then ordered alphabetically by author within each work category.

(252) From the twenty-one cohort and six case-control studies of uranium workers summerised in Table 3.1, several specific steps in the uranium nuclear cycle are covered: uranium milling and refining (Pinkerton et al., 2004; Boice et al., 2007, 2008; Zablotska et al,. 2013; Kreuzer et al., 2015; Bouet et al., 2018; Zablotska et al., 2018), uranium enrichment via gaseous diffusion (McGeoghegan et al., 2000; Yiin et al., 2009, 2017, 2018; Chan et al., 2010; Figgs et al., 2013; Zhivin et al., 2016), chemical conversion and fuel fabrication (Dupree-Ellis et al., 2000; McGeoghegan et al., 2000; Richardson and Wing, 2006; Guseva Canu et al., 2011; Silver et al., 2013; Bouet et al., 2019; Golden et al., 2019), and research and development of nuclear reactors and uranium and plutonium fuel fabrication (Ritz et al., 2000; Boice et al., 2011). Three studies covered all steps of the nuclear fuel cycle (Fournier et al., 2016; Samson et al., 2016; Grellier et al., 2017). The solubility of the uranium used in these different activities varied from predominantly soluble uranium in uranium enrichment to insoluble uranium in uranium processing.

(253) Very few studies provided information on uranium-specific health risks due to missing (or sparse) uranium-specific exposure estimates, because of absent or incomplete historical recording of individual information (Table 3.1). In this publication, we focus on studies that reported uranium-specific risks for the three most plausible cancer outcomes following uranium exposure: lung cancer (organ of entry following inhalation), kidney cancers (organ of accumulation and elimination), and leukaemia and other lympho-haematopoietic malignancies (outcome of interest after general radiation exposure).

(254) Studies of uranium millers are not informative with respect to cancer risks linked specifically to uranium-bearing dust (Table 3.1).

Table 3.1. Description of studies of workers where uranium was the major source of exposure.

N	Reference	Country	Facility	Work type	Study design	No. of workers	Relevance for uranium risk assessment
1	Boice et al. (2007)	USA	Uravan Colorado	U milling	cohort	571 all/450 likely internal radiation	no (only SMR)
2	Boice et al. (2008)	USA	Grants New Mexico	U milling	cohort	904 all/718 internal radiation	no (only SMR)
3	Bouet et al. (2018)	France	SIMO-SMJ (Lodève, les Bois Noirs, Bessines, L'Escarpière, Jouac)	U milling	cohort	1291	no (only SMR)
4	Kreuzer et al. (2015)	Germany	WISMUT	U milling	cohort	4054	no (exposure in kBqh/m^3)
5	Pinkerton et al. (2004)	USA	Colorado Plateau	U milling	cohort	1484	no (absence of the U-specific exposure metric)
6	Zablotska et al. (2013)	Canada	Port Hope	U milling	cohort	3000/2472 uranium	no (absence of the U-specific exposure metric)
7	Zablotska et al. (2018)	Canada, Germany	Port Hope WISMUT	U milling, U conversion	cohort	7431	no (exposure in WLM)
8	Guseva Canu et al. (2011)	France	AREVA NC Pierrelatte	U conversion	cohort	2897	yes
9	McGeoghegan and Binks, (2000a)	UK	Springfields	U conversion	cohort	19,454	no (absence of the U-specific exposure metric)

10	Chan et al. (2010)	USA	Paducah	U enrichment	cohort	6759	yes
11	Figgs (2013)	USA	Paducah	U enrichment	nested case-control	6820	No (absence of the U specific exposure metric)
12	Gillies and Haylock (2014)	UK	BNFL installations	U processing and enrichment	cohort	11,004	No (absence of U-specific doses)
13	McGeoghegan and Binks (2000b)	UK	Capenhurst	U enrichment	cohort	12,540	no (absence of the U-specific exposure metric)
14	Yiin et al. (2009)	USA	Oak Ridge K-25	U enrichment	nested case-control	588	yes
15	Yiin et al. (2017)	USA	Oak Ridge K-25, Paducah, Portsmouth	U enrichment	nested case-control	29,303	yes
16	Yiin et al. (2018)	USA	Oak Ridge K-25, Paducah, Portsmouth	U enrichment	nested case-control	29,303	yes
17	Zhivin et al. (2016)	France	Pierrelatte (AREVA NC, CEA, Eurodif)	U enrichment	cohort	4688	yes
18	Bouet et al. (2019)	France	COMURHEX, FBFC, CERCA, SOCATRI	U fuel fabrication, U conversion, waste processing	cohort	4541	yes
19	Dupree-Ellis et al. (2000)	USA	Mallinckrodt	U fuel fabrication, U conversion	cohort	2514	no (absence of the U-specific exposure metric)

20	Golden et al. (2019)	USA	Mallinckrodt	U fuel fabrication, U conversion	cohort	2514 all/1886 internal radiation	yes (update of Dupree-Ellis et al. 2000)
21	Richardson and Wing (2006)	USA	Oak Ridge Y-12	U fuel fabrication	nested case-control	3864	yes
22	Silver et al. (2013)	USA	Fernald Feed	U fuel fabrication	cohort	6409	yes
23	Boice et al. (2011)	USA	Rocketdyne	Radiation activities	cohort	46,970 all/2232 internal radiation	yes (multiple radionuclides, highest dose to U and Pu)
24	Ritz et al. (2000)	USA	Rocketdyne	Radiation activities	cohort	4607 all/2297 internal radiation	yes
25	Fournier et al. (2016)	France	French uranium nuclear fuel cycle	All steps, excluding U mining and milling	cohort	59,004	no (absence of U specific exposure metric)
26	Samson et al. (2016)	France	French uranium nuclear fuel cycle	All steps, excluding U mining and milling	cohort	12,649	no (only SMR)
27	Grellier et al. (2017)	Belgium, France, UK	SCK-CEN, Belgonucleaire, Belgoprocess, AREVA NC, CEA, UKAEA, AWE, BNFL	All steps starting from U conversion	nested case-control	1886	yes

Studies providing an estimate of the relationship between cancer risk and U exposure are printed in bold italic font.
SMR: Standardised Mortality Ratio; WLM: Working Level Month (cumulative exposure to radon decay products)

The Alpha-Risk study

(255) In the EU-funded Alpha-Risk project (Grellier et al., 2017), internal exposure to uranium and plutonium for workers in the British (AWE, UKAEA and BNFL cohorts), Belgian (SCK•CEN/BN cohort) and French (CEA-COGEMA cohort) nuclear industries was investigated through a case-control study of lung cancer and leukaemia mortality, nested within appropriate cohorts from the International Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry. The nested case-control design allowed detailed dose reconstruction as well as the collection of individual data on potential confounders.

(256) Grellier et al. (2017) found a lung cancer mortality Excess Odds Ratio (EOR) per Gy of lung dose from uranium alpha-particles for all workers included in the Alpha-Risk study (median lung dose in 1011 controls, 2.22 mGy) of 4.2 (90% CI: -2.5, 17). There is notable variation in the EOR/Gy estimates when each contributing cohort is removed from the analysis: the highest EOR/Gy was obtained when the BNFL workforce (median lung dose in 781 controls, 2.38 mGy) was excluded, EOR/Gy = 26 (90% CI: 2.5, 80), while the lowest EOR/Gy estimate was obtained when the AWE cohort (median lung dose in 125 controls, 3.25 mGy) was removed to give an EOR/Gy of -0.1 (90% CI: -3.3, 9.3).

(257) As indicated in section 2.3.2, the EOR/Gy of lung dose from plutonium for all workers included in the Alpha-Risk study (median lung dose in 463 controls, 1.25 mGy) was 49 (90% CI: 16, 106), about ten times larger than that for the dose to the lung from uranium, while the estimated lung cancer risk associated with gamma radiation (median dose in 1264 controls, 33.86 mGy) was EOR/Gy = -0.44 (90% CI: -0.6, 0.04) (Grellier et al., 2017).

(258) The results from the Alpha-Risk study for leukaemia mortality have yet to be published.

3.3.2. Statistical methods

(259) The cohort and case-control studies summarised in Table 3.1 were mainly based on causes of death information obtained from death records, although a few also used cancer registration data. All the cohort studies reported SMRs (standardised mortality ratios) and some also SRRs (standardised registration ratios).

(260) In the majority of studies, the referent was the national population although in some studies both national and regional referent rates were used. The expected number of deaths (or cancer registrations) were generally calculated adjusting for age, sex, race, and calendar period.

(261) For intra-cohort analyses, three analytic approaches were used: conditional logistic regression, Poisson modelling and Cox proportional hazards modelling. As examples, Ritz et al. (2000) used conditional logistic regression to estimate relative risks (RRs) adjusting for age at risk, pay status (as an indicator of socio-economic status), time since first exposure and external radiation dose.;Poisson modelling was used to estimate the ERR or RR. In their studies, Boice et al. (2011), Guseva Canu et al. (2011) and Golden et al. (2019) calculated risk estimates based on Cox proportional hazards modelling including age, sex, calendar time, and socio-economic status in the model; the referent group was unexposed workers. Chan et al. (2010) calculated standardised rate ratios using the direct standardisation method with the lowest exposed group as the referent. Zhivin et al. (2016) and Bouet et al. (2019) used grouped Poisson regression adjusted for sex, age, calendar period, socio-professional status, sub-cohort, and concomitant exposures to trichloroethene, heat, and noise.

(262) Three of the case-control studies used conditional logistic regression to estimate risk (Richardson and Wing, 2006; Yiin et al., 2009; Grellier et al., 2017). Risk sets were formed using incidence density matching with replacement based on attained age of the case. Richardson and Wing (2006) matched controls to the case on birth year, sex, race, socioeconomic status, length of employment and employment status at the attained age at death of the case; Yiin et al. (2009) selected 5 controls from the risk set for each case matched on sex, race and lived as long as the case; and Grellier et al. (2017) selected one to three controls matched on age, sex and facility. Yiin et al. (2017, 2018) used Cox proportional hazards analysis to estimate risk. For each outcome, risk sets were drawn from the cohort using incidence density matching on sex, race, attained age, birth date, and plant of the case.

3.3.3. Results by organ system

3.3.3.1. Lung cancer

(263) Studies of occupational exposure to uranium do not generate reliable findings unless cancer risks can be expressed in terms of organ/tissue-specific doses from internally deposited uranium. Many studies that include uranium workers do not use uranium doses, but 11 studies that have examined the association between lung cancer have employed uranium internal doses or dose proxies (Richardson et al., 2006; Chan et al., 2010; Guseva Canu et al., 2010; Boice et al., 2011; Silver et al., 2013; Zhivin et al., 2016; Grellier et al., 2017; Yiin et al., 2017; Bouet et al., 2019). These quantitative results are presented in Table 3.2.

Table 3.2. Dose-response analyses of uranium-specific lung doses and lung cancer risk.

N	Reference	No. of deaths	Unit of uranium exposure	Risk estimate per unit of exposure
1	Boice et al. (2011)	1463	Organ-specific internal dose, mSv	<5 mSv, RR = 0.98 (95% CI 0.81 to 1.20) 5-<10 mSv, RR = 1.00 (95% CI 0.65 to 1.54) 10-<50 mSv, RR = 0.93 (95% CI 0.63 to 1.36) 50-<100 mSv, RR = can't be calculated, n=0 100-<200 mSv, RR = can't be calculated, n=0 200+ mSv, RR = 1.64 (95% CI 0.74 to 3.65)
2	Bouet et al. (2019)	35	Internal lung U dose, mGy	ERR/mGy = - 0.02 (95% CI up to 0.01 with no estimated CI lower bound); no convergence after adjustment for smoking status
3	Chan et al. (2010)	129	Internal U exposure, µg.year^{-1}	21-50 µg.year^{-1}, RR=0.91 (95% CI 0.51 to 1.62) 51-125 µg.year^{-1}, RR=0.95 (95% CI 0.56 to 1.63) >125 µg.year^{-1}, RR=0.51 (0.30 to 0.88)

N	Reference	No. of deaths	Unit of uranium exposure	Risk estimate per unit of exposure
4	Guseva Canu et al. (2011)	53	Reprocessed uranium, Cumulative exposure duration (years)	Type F, HR=1.07 (95% CI 0.96 to 1.19) Type M, HR=1.13 (95% CI 1.03 to 1.25) Type S, HR=1.13 (95% CI 1.01 to 1.25)
5	Golden et al. (2019)	157	Organ specific internal dose, mGy	ERR/100 mGy = - 0.06 (95% CI - 0.18 to 1.12)
6	Grellier et al. (2017)	553	Total U alpha dose, Gy	EOR/Gy = 4.2 (90% CI - 2.5 to 17) or 5.3 (90% CI – 1.9 to 18) adjusted for smoking and socio-economic status
7	Richardson et al. (2006)	111	Internal dose, mSv	10-49.9 mSv, RR = 1.52 (95% CI 0.74 to 3.13) 50-99.9 mSv, RR = 1.20 (95% CI 0.54 to 2.67) 100+ mSv, RR = 1.40 (0.65 to 3.01)
8	Ritz et al. (2000)	44	Internal lung dose, mSv	RR/ 10 mSv = 0.74 (95% CI 0.29-1.92)
9	Silver et al. (2013)	269	Internal U dose, mGy	ERR/mGy = 0.022 (95% CI - 0.009 to 0.07)
10	Yiin et al. (2017)	293	Internal U dose, mGy	ERR/mGy = - 0.75 (95% CI - 2.31 to 1.12)
11	Zhivin et al. (2016)	100	Natural soluble U exposure categories	Low, RR = 1.2 (95% CI 0.64 to 2.05) Medium, RR = 0.92 (95% CI 0.54 to 1.6) High, RR = 0.74 (95% CI 0.42 to 1.3)

(264) The majority of selected studies have shown no increase in lung cancer risk with lung dose from uranium. A single French study (Guseva Canu et al., 2011) revealed significant increases for exposure to reprocessed but not unirradiated uranium. Studies of cohorts of uranium enrichment workers in France (Zhivin et al., 2016) and in the USA (Yiin et al., 2017), exposed mostly to rapidly soluble uranium compounds, did not find statistically significant lung cancer risks. The study by Ritz et al. (2000) is the only one with a statistically significant dose-response relationship; the exposure of this cohort was to a mixture of radioisotopes.

(265) The studies of Grellier et al. (2017) and of Silver et al. (2013) indicate a positive dose response relationship, but both with a large confidence interval that cannot exclude the absence of a trend with uranium dose. In the Alpha-Risk study of Grellier et al. (2017), when testing the influence of specific employer groups, the risk coefficients for AWE and BNFL were in opposite directions.

(266) For most of the workers included in these studies, the estimates of mean lung dose were very low. In the study by Yiin et al. (2017), the average absorbed lung dose linked to uranium exposure was 0.07 mGy, while the cumulative external gamma dose to the lung was 40 mGy. In the case-control study of Grellier et al. (2017), the median lung dose from uranium was 2.2 mGy (with a maximum value of 301.5 mGy), while the mean dose from gamma radiation was 33.9 mGy. The study by Golden et al. (2019) reported a median lung dose of 33.1 mGy with a maximum value of 885.2 mGy (Ellis et al., 2017). The study by Bouet et al. (2019)

reported a mean lung dose from uranium of 4.22 to 10.9 mGy, depending on modelling hypotheses, while the cumulative external gamma dose to the lung was 11.12 mGy.

(267) In order to increase the statistical power and take into account uncertainty linked to the estimated individual doses from uranium exposure, a large international effort with a common protocol for data collection; for organ dose calculations focusing on those uranium oxide components that may contribute substantially to the lung dose; and for appropriate analysis of results, is necessary to achieve a better estimate of the lung cancer risk from uranium exposure.

3.3.3.2. Lymphatic and haematopoietic cancers

(268) Results related to uranium-specific doses and risk of lymphatic and haematopoietic cancers are presented in Table 3.3. Among the 16 selected studies, results are presented using the malignant disease groupings of leukaemia, other lympho-haematopoietic cancers (non-Hodgkin lymphoma (NHL) and multiple myeloma (MM)), and all lympho-haematopoietic cancers combined (LHP). Three studies by Yiin et al. (2009, 2017, 2018) of uranium enrichment workers consistently reported a significantly increased risk of multiple myeloma. For the other three groupings, no increase in risk was observed with exposure to uranium.

(269) The issues considered above for the lung cancer studies apply to these studies as well. An additional difficulty in comparing these studies is the grouping of outcomes in multiple ways: all lympho-haematopoietic cancers (LHP), non-Hodgkin lymphoma (NHL), multiple myeloma (MM), and others. Not only are there multiple groupings but the ICD codes used to define each grouping may not be the same across studies.

Table 3.3. Dose-response analyses of uranium exposure and lymphatic and haematopoietic cancer risk.

N	Reference	No. of deaths	Unit of uranium exposure	Risk estimate per unit of exposure
			Leukaemia	
1	Boice et al. (2011)	151	Organ-specific internal dose, mSv	<5 mSv, RR = 0.91 (95% CI 0.50 to 1.64) 5-<10 mSv, RR = 0.95 (95% CI 0.27 to 3.29) 10-<50 mSv, RR = 0.66 (95% CI (0.26 to 1.66) 50-<100 mSv, RR = 1.38 (95% CI 0.45 to 4.17) 100-<200 mSv, RR = can't be calculated, n=0 200+ mSv, RR = can't be calculated, n=0
2	Chan et al. (2010)	21	Internal U exposure, µg year^{-1}	21-50 µg year^{-1}, RR = 0.73 (95% CI 0.18 to 3.01) 51-125 µg year^{-1}, RR = 0.49 (95% CI 0.11 to 2.26) >125 µg year^{-1}, RR = 0.77 (95% CI 0.24 to 2.50)

N	Reference	No. of deaths	Unit of uranium exposure	Risk estimate per unit of exposure
3	Golden et al. (2019)	18	Organ specific internal dose, mGy	ERR/ 100 mGy = - 0.14 (95% CI – 0.60 to 0.33)
4	Silver et al. (2013)	35	Organ-specific internal dose, µGy	ERR/0.1 mGy = - 0.061 (95% CI NA to 0.25)
5	Yiin et al. (2017)	117	Organ-specific internal dose, mGy	ERR/mGy = 0.39 (95% CI - 0.70 to 2.32)
6	Yiin et al. (2018)	111	Organ-specific internal dose, mGy	50th %ile (0.09 mGy) RR=1.08 (95% CI 0.96 to 1.13); 75th %ile (0.27 mGy) RR=1.24 (95% CI 0.87 to 1.94)
			Other lympho-haematopoietic cancers	
7	Boice et al. (2011)	491 (LHP)	Organ-specific internal dose, mSv	<5 mSv, RR = 0.85 (95% CI 0.60 to 1.19) 5-<10 mSv, RR = 1.67 (95% CI 0.94 to 3.00) 10-<50 mSv, RR = 1.30 (95% CI (0.41 to 4.09) 50-<100 mSv, RR = 4.21 (95% CI 0.45 to 14.0) 100-<200 mSv, RR = can't be calculated, n=0 200+ mSv, RR = can't be calculated, n=0
8	Bouet et al. (2019)	12	Liver internal dose as proxy for all systemic organ doses, mGy	ERR/mGy = - 1.27 (95% CI up to 14.72 with no estimated CI lower bound)
9	Chan et al. (2010)	26 (NHL)	Internal U exposure, µg year^{-1}	21-50 µg year^{-1}, RR = 9.95 (95% CI 1.22 to 81.26) 51-125 µg year^{-1}, RR = 8.85 (95% CI 1.11 to 70.83) >125 µg year^{-1}, RR = 5.74 (95% CI 0.72 to 45.48)
		57 (LHP)	Internal U exposure, µg year^{-1}	21-50 µg year^{-1}, RR = 1.79 (95% CI 0.66 to 4.88) 51-125 µg year^{-1}, RR = 1.48 (95% CI 0.55 to 4.02) >125 µg year^{-1}, RR = 1.35 (95% CI 0.53 to 3.41)
10	Golden et al. (2019)	30 (NHL)	Organ specific internal dose, mGy	ERR/100 mGy = 0.20 (95% CI – 0.23 to 0.64)
11	Ritz et al. (2000)	10 (LHP)	Internal lung dose, mSv	RR/10 mSv – 1.23 (95% CI 0.97 to 1.55)

N	Reference	No. of deaths	Unit of uranium exposure	Risk estimate per unit of exposure
12	Silver et al. (2013)	32 (NHL)	Organ-specific internal dose, µGy	ERR/100 µGy = 0.33 (95% CI - 0.065 to 1.6)
13	Yiin et al. (2009)	98 (MM)	Organ-specific internal dose, µGy	OR/10 µGy = 1.04 (95% CI 1.00 to 1.09)
14	Yiin et al. (2017)	163 (NHL)	Organ-specific internal dose, mGy	ERR/mGy = - 0.14 (95% CI - 0.85 to 0.97)
		69 (MM)	Organ-specific internal dose, mGy	ERR/mGy = 2.92 (95% CI 0.51 to 7.86)
15	Yiin et al. (2018)	151 (NHL)	Organ-specific internal dose, mGy	50^{th} %ile (0.09 mGy) RR=0.99 (95% CI 0.92 to 1.12); 75^{th} %ile (0.27 mGy) RR=0.96 (95% CI 0.75 to 1.38)
		65 (MM)	Organ-specific internal dose, mGy	50^{th} %ile (0.09 mGy) RR=1.78 (95% CI 1.11 to 3.80); 75^{th} %ile (0.27 mGy) RR=3.42 (95% CI 1.35 to 9.64)
16	Zhivin et al. (2016)	28 (LHP)	Natural soluble U exposure categories	Low, RR = 1.7 (95% CI 0.48 to 5.5) Medium, RR = 1.4 (95% CI 0.52 to 3.9) High, RR = 1.08 (95% CI 0.37 to 3.3)

3.3.3.3. Kidney cancer

(270) Toxicological data show that uranium causes damage to the kidneys after acute high-level exposure, owing to uranium being a heavy metal that preferentially accumulates in, and is eliminated from the body via, the kidneys. The studies presented in Table 3.4 cannot clearly confirm a carcinogenic effect at low chronic exposure; even though a number of studies indicate a positive trend, the large confidence intervals include the possibility of the absence of an effect.

(271) A single study by Golden et al. (2019) revealed a significant positive dose-response relationship. When the toxicological effect of uranium was considered by controlling for the level of dust exposure encountered by the workers, the risk increased with an HR=1.85 (95% CI 1.09 to 3.14). The dose-response relationship over cumulative dust categories was not significant. The type of kidney cancer linked to radiation exposure is located in the renal pelvis and ureter (primarily transitional cell carcinomas) and not in the renal parenchyma, except at very high therapeutic doses. No renal pelvis cancers were observed and only one cancer of the ureter among the reported deaths from kidney cancer.

(272) Improvement should be possible in the future via considering the heterogeneity of the distribution of uranium in the different parts of the kidney, and identifying the part of the kidney where the cancer occurs since these may differ for radiation versus chemically associated effects.

Table 3.4. Dose-response analyses of uranium exposure and kidney cancer risk

N	Reference	No. of deaths	Unit of uranium exposure	Risk estimate per unit of exposure
1	Boice et al. (2011)	121	Organ-specific internal dose, mSv	<5 mSv, RR = 0.96 (95% CI 0.49 to 1.88) 5-<10 mSv, RR = 0.69 (95% CI 0.21 to 2.27) 10-<50 mSv, RR = can't be calculated, n=0 50-<100 mSv, RR = 2.63 (95% CI 0.64 to 10.7) 100-<200 mSv, RR = can't be calculated, n=0 200+ mSv, RR = can't be calculated, n=0
2	Golden et al. (2019)	22	Organ specific internal dose, mGy	HR/ 100 mGy = 1.73 (95% CI 1.07 to 2.79)
3	Ritz et al. (2000)	8 (bladder and kidney)	Internal lung dose, mSv	RR/10 mSv = 0.19 (95% CI 0.00 to 20.8)
4	Silver et al. (2013)	15	Organ-specific internal dose, µGy	ERR/0.1 mGy = 0.033 (95% CI -0.021 to 0.50)
5	Yiin et al. (2017)	110	Internal U dose, mGy	ERR/mGy = 0.14 (95% CI - 0.16 to 0.66)
6	Yiin et al. (2018)	101	Internal U dose, mGy	50^{th} %ile (0.30 mGy) RR=1.28 (95% CI 0.94 to 2.06); 75^{th} %ile (0.93 mGy) RR=1.86 (95% CI 0.83 to 4.30)

3.3.4. Discussion

3.3.4.1. Summary of results from studies of workers

(273) At present, there is only weak epidemiological evidence to suggest an association between internal radiation dose resulting from exposure to uranium and risk of cancers that have been studied. However, the size of the study populations limits the statistical power to detect an association and the organ doses are relatively low in most studies. The main limitation is the lack of precise estimates of internal uranium-specific dose to the individuals.

(274) Contrary to the situation for plutonium, present knowledge of cancer risks associated with uranium exposure does not permit a lifetime cancer risk calculation.

(275) Several statistically significant positive results have been reported in studies of uranium workers. One study suggested a positive association between insoluble forms of reprocessed uranium and lung cancer (Guseva Canu et al., 2011) on the basis of a job exposure matrix. Ritz (1999) reported an increased RR for lung cancer mortality among workers with ≥200 mSv of internal dose lagged 15 years when external exposure was 50 mSv or greater. Grellier et al. (2017) and Silver et al. (2013) showed a positive trend between the lung dose

estimated from chronic uranium exposure and lung cancer risk, but the confidence intervals of these positive trends did not exclude the absence of a trend. In future, the study of lung cancer risk should focus primarily on workers being exposed to insoluble uranium oxide since these workers will have received the largest lung doses. Smoking habits should also be taken into account if information is available.

(276) Among gaseous diffusion plant workers, there is a suggestion of an increase of various types of lymphatic and haematopoietic cancers, although not leukaemia. Yiin et al. (2009, 2017, 2018) found an increased risk for multiple myeloma associated with red bone marrow dose, after adjusting for external radiation resulting from occupational chest x-rays and film badge records. Chan et al. (2010) reported an increased risk of non-Hodgkin lymphoma among gaseous diffusion plant workers exposed to uranium.

(277) Positive results have been reported for kidney cancer in various parts of the nuclear fuel cycle. Golden et al. (2019) reported a significant dose-response relationship and Silver et al. (2013) showed a positive trend among uranium processing workers. Yiin et al. (2017, 2018) found a positive trend among gaseous diffusion plant workers, but the wide confidence intervals did not exclude the absence of a trend.

(278) Overall, epidemiological studies of uranium workers do not provide convincing evidence of a rasied cancer risk that can be attributed to uranium exposure. Even studies of lung cancer following inhalation of insoluble compounds of uranium, which lead to the highest lung doses from uranium, have provided inconclusive evidence, and the results from studies of other sites of cancer do not provide a consistent pattern of findings. Further high quality studies are required to improve this situation.

3.3.4.2. Summary of results from studies of uranium in drinking water

(279) The evidence for uranium carcinogenicity linked to ingestion remains limited. In a review of epidemiological studies of possible health effects after ingesting naturally-occurring radionuclides through drinking-water, Guseva Canu et al. (2012) considered 27 peer-reviewed articles published between 1970 and 2009 reporting original results, including studies of uranium, radium and radon in drinking-water. Among these, 5 provided results on a potential association between cancer risk and uranium concentration. A Canadian case-control study of Non-Hodgkin lymphoma found higher uranium concentrations in the drinking-water of cases than of controls (Withmans et al., 2008; 88 cases/132 controls). A case-control study of leukaemia cases in Fallon (USA) found no significant differences in well uranium or radon concentration between cases and controls (Seiler, 2004; 16 cases wells/100 other wells). The only cohort study was conducted among Finnish individuals using bedrock well water. On the basis of this cohort, 3 case-cohort studies were conducted, using individual level exposure assessments, on 35 leukaemia cases (Auvinen, 2002), 107 stomach cancer cases (Auvinen, 2005) and 112 urinary cancer cases, including kidney cancer (Kurttio, 2006b). No significant associations were reported, either with radionuclide concentrations in well water (uranium, radium and radon) or with cumulative radiation doses when estimated.

(280) Weak but statistically significant associations between uranium concentration in drinking water and cancers have been observed in ecological studies in Bavaria (Banning and Benfer, 2017) and in South Carolina (Wagner et al., 2011).

(281) The available results do not show an association between uranium in drinking water and cancer risk. However, only few studies have been conducted up to now, and methodological limitations (poor exposure measurement methods, no control for confounding, small sample size) affect most of them.

(282) The effects of exposure to depleted uranium have received attention in extensive reviews of the health of the Gulf War veterans (Harley, 1999; Royal Society, 2001, 2002; Depleted Uranium Oversight Board, 2007; Committee on Gulf War and Health, 2008). No excess cancer risk has been identified among those individuals exposed to depleted uranium.

3.3.4.3. Complexity of exposure and dose reconstruction

(283) Differences in the solubility of uranium and methods used to measure uranium-specific doses complicate the interpretation of results with respect to internal uranium exposure. Studies have included workers employed in uranium processing and reprocessing operations, where the solubility of the uranium ranged from very soluble to insoluble.

(284) In their case-control study of multiple myeloma, Yiin et al. (2009) assigned absorbed doses to the specific organ of interest, namely the red bone marrow; red bone marrow doses from photofluorographic chest x rays documented in the workers' occupational medical records were included as a separate variable in analyses. Boice et al. (2006a,b) used ICRP biokinetic models from current or upcoming ICRP reports to estimate annual equivalent doses to 16 specific organs or tissues taking into account time of exposure, type of radionuclide, and excretion patterns. Other studies included an estimate of internal radiation exposure but not the calculation of doses to target organs. Ritz (1999) estimated lung dose based on uranium urinalysis results and used this dose as a surrogate for all organs of interest. Guseva Canu et al. (2010) estimated exposure to uranium based on a job exposure matrix where different uranium compounds were distinguished by their absorption types (F, M and S) and their isotopic composition (natural uranium and reprocessed uranium bearing compounds). Chan et al. (2010) also used uranium urinalysis results but reported cumulative excretion as microgram-years (µg.y). The use of µg.y as a measure of internal exposure is questionable since it depends on the frequency of monitoring. During recent years, more studies have provided estimates of organ/tissue-specific doses from uranium. In the Alpha-Risk case-control study, Grellier et al. (2017) assigned best estimates of individual organ/tissue doses. In a study combining cohorts of gaseous diffusion plant workers (Yiin et al., 2017, 2018), organ/tissue doses were calculated using extensive uranium urinalysis data along with uranium gravimetric and radioactivity concentration data and estimates of enrichment levels of uranium to which workers may have been exposed (Anderson et al., 2017). Ellis et al. (2018) described the methodology that was used to update the Mallinckrodt Chemical Works uranium processing workers cohort following the framework outlined by Bouville et al. (2015).

(285) The calculations of external radiation exposure for the uranium workers studies were similar to those used for the plutonium worker studies in terms of the variability in the methods used. Most cohort studies limited external exposure to recorded exposure to gamma and x rays at the site. In addition to external radiation monitoring records from the site, Boice et al. (2006a,b, 2011), Golden et al. (2019) and Yiin et al. (2009) included these records from other sites and databases. Yiin et al. (2009) included only gamma and x rays, while Richardson and Wing (2006) included tritium; all three imputed exposures for missing records.

3.3.4.4. Recommendations for future studies

(286) The information from current epidemiological studies of uranium exposure is insufficient to reliably quantify dose-response relationships. More studies are needed before any estimate of risk and detriment can be envisaged.

(287) Work is already ongoing to enable future combined studies of uranium workers which will greatly improve the statistical power of the studies. The protocol of an international Pooled Analysis of Uranium Processing Workers (iPAUW), including cohorts from the USA, Europe and possibly other countries, is currently being developed. More than 15 cohorts including 100,000 uranium processing workers are potentially eligible for inclusion. As part of this project, a dosimetric protocol aiming to harmonise uranium exposure information and organ/tissue-specific dose calculations across cohorts is being developed. The improved statistical power of this analysis will allow the proposed collaborative study to have greater ability to characterise potential risks associated with occupational uranium exposure.

(288) In the US, work is progressing on the Epidemiologic Study of One Million Persons. A component of this study includes Department of Energy nuclear workers who have been exposed to uranium (and plutonium) (Boice et al., 2018). Over 360,000 workers employed at 15 Department of Energy and its predecessor facilities have been identified. The goal of the pilot project is to characterise these workers with regard to vital status follow-up, external dose and potential for internal intakes. The focus of the effort will be on those workers already included in a retrospective cohort mortality study. Vital status is being updated using a common protocol. Bioassay and external radiation monitoring data have been computerised, and the methodology that will be used to perform the organ/tissue-specific dose estimations has been established (Bouville et al., 2015). A pooled analysis of about 13,000 North American workers involved in uranium milling and processing is currently underway. The methods being used are very similar to those used in the One Million Persons study.

4. CONCLUSION

(289) The risks of cancer following exposure to the alpha-particle emitting isotopes of plutonium and uranium have been evaluated in the present publication, which is complementary to *Publication 115* (ICRP, 2010a) focussing on radon and its decay products. The publication updates previous reviews published by international committees on exposure to plutonium and uranium, especially the IARC monograph on internal emitters in 2012 (IARC, 2012) and Annex D of the UNSCEAR 2016 Report on the biological effects of exposure to uranium (UNSCEAR, 2017), but also the BEIR IV Report (NRC, 1988). The close collaborative work between experts of ICRP Committee 1 and Committee 2 and other experts with competences in epidemiology or dosimetry was key for preparing this report, which constitutes the first comprehensive review of health risks associated with plutonium exposure for over 30 years.

(290) Compared to radon and its decay products, the epidemiological evidence on risks associated with exposure to plutonium is less extensive. Indeed, the first epidemiological results from underground hard-rock miner studies were published towards the end of the 1960s whereas most of the results related to plutonium were published after the 1990s. Further, the number of studies providing reliable results on plutonium-specific risks is limited to a few studies (essentially, the Mayak and Sellafield worker cohorts), whereas about 20 cohorts of miners have been studied, plus several tens of indoor radon studies in the general population. In addition, the assessment of doses due to plutonium exposure is complicated by the chemical nature of plutonium compounds, which plays a major role in determining lung solubility, and presents difficulties in the reconstruction of lung doses from bioassay measurements of plutonium concentrations in urine or faeces. These differences may partly explain the fact that results on plutonium-related risks are presently less consistent than those related to radon. The situation is more striking for uranium-specific risks, the information currently available from epidemiological studies being insufficient to provide reliable estimates of risk, especially due to limits in exposure reconstruction. Further studies with improved internal dosimetry are needed.

(291) Most of the cohorts of workers studied had a long follow-up (over several decades). A good understanding of the dosimetric approaches used in the past, or of surrogates such as job-exposure matrix approaches, was necessary to evaluate the quality and reliability of the individual annual organ/tissue-specific doses used in the epidemiological analyses. The number and quality of bioassay measurements per individual, the quality of environmental measurements, and the solubility of the inhaled radionuclide and its chemical compounds, are some of the factors that influence the quality of estimates of the organ/tissue-specific dose over time.

(292) Cancer risk resulting from plutonium exposure has been examined through studies of Russian, American and European workers, which include a wide range of exposure levels. The two most informative cohorts of plutonium workers are those employed at the Mayak plant in the Russian Federation and at the Sellafield plant in the UK. Assessments of intakes and resulting organ/tissue doses for workers arising from the inhalation of plutonium (principally ^{239}Pu) have been based primarily on the interpretation of individual urine bioassay data, taking account of the workers' occupational histories and the physicochemical forms of the inhaled plutonium aerosols. Results from autopsy data have also been used to determine model parameter values. Biokinetic and dosimetric models have been continuously improved over the last 20 years, but significant uncertainties remain in the assessed doses. The epidemiological

studies of plutonium workers provide results that allow quantitative estimation of lung cancer risk related to alpha-particle dose. For cancer risks other than lung, associations between plutonium exposure and risk of liver and bone cancer were also observed in the Mayak studies, as would be anticipated from the preferential deposition of plutonium on bone surfaces and in the liver. There is no consistent evidence of a positive dose response between leukaemia risk and plutonium exposure.

(293) Calculations have been conducted of the lifetime excess risk of lung cancer mortality associated with lung absorbed dose, based on scenarios of inhalation of a total plutonium intake of 1 Bq, assuming either an acute intake or a chronic intake, of either soluble plutonium nitrate or insoluble plutonium oxide. These unitary intake scenarios should be considered as examples, to provide an order of magnitude of the risk, and to illustrate variations in the dose and risk for a unitary intake.

(294) Comparing the lifetime excess risk of lung cancer mortality risk from exposure to external gamma radiation (based on the Life Span Study of Japanese A-bomb survivors) and from internal exposure to plutonium alpha particles (based on the Mayak workers study), it was found that, for the same lung absorbed dose, the risk from plutonium alpha-particle exposure is larger than the risk from external gamma-ray exposure by factors of about 15 to 16 and 19 to 22 when based on the Life Span Study ERR model and EAR model, respectively, depending on the exposure scenario. Despite the very different dose distribution of plutonium and radon progeny within the lung, a similar calculation for radon progeny exposure produced factors based on the ERR model of about 14 to 15. These results suggest a biological effectiveness of alpha particles relative to high energy photons equal to about 14 to 16 for lung cancer.

(295) These values are compatible with the current radiation weighting factor (w_R) of 20 used for the purposes of radiological protection by the Commission for alpha particles in the calculation of equivalent and effective doses (ICRP, 2007). Nevertheless, it should be noted that this comparison is based on lung absorbed dose and lifetime excess risk of lung cancer mortality, with an application of a DDREF of 2 to the risk derived from the Japanese Life Span Study. Not applying a DDREF would lead to a relative biological effectiveness of about 7 to 8. Also, this comparison of the effects of plutonium exposure and external gamma exposure is based on the lifetime risk of lung cancer mortality, and not on radiation detriment. Meanwhile the w_R is a judgement value for radiological protection purposes and applies to all stochastic effects of alpha radiation, including other types of cancer. Plutonium related risks have been observed for liver and bone for which different RBEs for alpha radiation may apply.

(296) The review of recently published epidemiological studies of cancer risk from exposure to uranium updated the UNSCEAR 2016 Report (UNSCEAR, 2017). Most studies did not use uranium-specific doses to organs/tissues derived from monitoring results and considered exposure through environmental indicators, job-exposure matrices, or expressed the risk in relation to external radiation exposure. A few studies published in recent years used improved organ/tissue-specific uranium dose calculations, but they remain inconclusive because statistical power was limited or because some of the information needed to reconstruct doses was not recorded in the past. Relatively fast clearance of uranium from blood circulation, variability of exposure to uranium compounds and differences in the methods used to monitor internal exposure to uranium complicate the dosimetry of workers employed in uranium processing, concentration, enrichment and reprocessing operations. The solubility of the uranium compounds to which workers are exposed is an especially important parameter in determining lung doses from bioassay data. In summary, with the information from currently

available epidemiological studies, there are insufficient data to reliably estimate the dose-response relationships between uranium exposure and any cancer site.

(297) Uncertainties associated with uranium and plutonium exposure and dose reconstruction are important, and different chemical forms can lead to very different cumulative organ/tissue-specific absorbed doses per Bq intake. Concerted efforts have been made in recent years to improve organ/tissue-specific dose assessment and to consider the potential impact of uncertainty on risk estimates. Continuation of such efforts and consideration of improved dosimetric approaches is recommended for future research, as the radioisotopes of these two elements continue to be of major importance for some groups of workers in the nuclear industry. Further research is needed to improve assessment of health risks associated to plutonium or uranium exposure, in epidemiology, dosimetry and risk modelling. Important efforts have been made in recent years to improve dose assessment and to consider the potential impact of uncertainties on risk estimates, and should be maintained in the future. Also, extension of existing cohorts and combined analyses of data are needed to increase power and allow a better estimation of the risks associated with plutonium and uranium exposures. Future research may better characterise the risks associated with alpha particles emitted by plutonium for cancer induction in organs other than lung. For uranium, distinction of the different chemical forms of uranium componds in future analyses is highly desirable. Future pooled analyses are expected to provide additional information on potential risks associated with uranium exposure.

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3273

ANNEX A. RISK OF CIRCULATORY DISEASES FROM EXPOSURES TO PLUTONIUM AND URANIUM

(A 1) In addition to cancer risks, several epidemiological studies of populations exposed to plutonium or uranium also considered other health effects, and especially diseases of the circulatory system (CD). Being outside of the scope of the present report, these results are summarized in the present annex.

A.1. Plutonium exposure and risk of circulatory diseases

(A 2) The incidence and mortality risks from CD have been analysed in the cohort of Mayak workers. The first study (Azizova et al., 2010a,b) considered a cohort of 12,210 Mayak workers first employed at one of the main facilities during the first ten years of operations (1948–1958). This period corresponded to the first years of Mayak operations, when workers were exposed to high doses of both external gamma rays and internal alpha-particle radiation due to plutonium intake. This study showed a statistically significant effect of external and internal plutonium exposures on CD. Further analyses of both ischemic heart disease (IHD) (Azizova et al., 2012) and cerebrovascular diseases (CeVD) (Azizova et al., 2011) were performed in an expanded Mayak cohort with an additional 6553 workers first employed in 1959-1972. The cohort included 18,763 workers (25% females) first employed at one of the main facilities of Mayak (i.e. reactors, radiochemical and plutonium plants), in 1948-1972. Workers employed at radiochemical and plutonium production facilities could be exposed to both external gamma rays and internal alpha-particle radiation from incorporated plutonium. Liver absorbed doses were estimated using the respiratory tract model described by Khokhryakov et al. (2005), and the systemic model for plutonium of Leggett et al. (2005). Follow-up was extended up to the end of 2005. The numbers of observed cases (deaths) were 6134 (2629) for IHD and 7326 (1495) for CeVD. Data on non-radiation CD risk factors such as smoking (available for 91.5% of workers), alcohol consumption (86.5%), blood pressure (95.2%), and body mass index (79.6%) were collected.

(A 3) A statistically significant increasing trend was demonstrated for CeVD incidence with increasing total internal alpha-particle dose to liver. The estimated ERR/Gy increased with increasing lag period. The relationship persisted after adjustment for body mass index, employment duration and external radiation exposure. The evidence for this trend related mainly to males rather than females (p-value for interaction < 0.001) as well as radiochemical rather than plutonium facility workers (p-value for interaction $= 0.001$). Notably, there was no statistically significant trend in CeVD mortality (rather than incidence) in relation to internal alpha-particle liver dose.

(A 4) No statistically significant trend was observed for IHD incidence with absorbed dose to liver from internal alpha-particle radiation, either with or without adjustment for external gamma-ray dose. For IHD mortality, an increasing trend was observed with liver dose from internal alpha-particle exposure, but the estimated ERR/Gy became lower and statistically non-significant after adjustment for external exposure.

(A 5) The SOLO project considered CD mortality in the Mayak and Sellafield cohorts, and where appropriate (i.e. in the absence of significant heterogeneity between the two cohorts) in the combined cohort (Azizova et al., 2018). The study examined CD as a whole, and also separately IHD and CeVD mortality. Doses used in the analyses were the cumulative external Hp(10) dose and the cumulative absorbed dose to the liver from alpha-particles emitted by

deposited plutonium. In respect of external dose, the ERR/Sv estimates were significantly raised for both worker cohorts (marginally so for Mayak) for CD and IHD (but not for CeVD), but differed significantly between the two cohorts, the estimate for the SWC being approximately ten times greater than that for the MWC. In respect of the internal liver dose from plutonium, the ERR/Gy estimates did not differ significantly from zero for either the Mayak, Sellafield or the pooled plutonium worker cohorts (PuWC) for mortality from CD, IHD or CeVD – for CD, the ERR/Gy estimates were 0.03 (95% CI: -0.07, 0.17) for the MWC, 1.06 (95% CI: <0, 3.49) for the SWC, and 0.04 (95% CI: -0.06, 0.18) for the PuWC; for IHD, +0.00 (95% CI: <0, 0.20), 0.61 (95% CI: <0, 3.12), and 0.02 (95% CI: <0, 0.22), respectively; and for CeVD, 0.07 (95% CI: <0, 0.37), 3.75 (95% CI: <0, 12.44, and 0.08 (95% CI: <0, 12.44), respectively.

A.2. Uranium exposure and risk of circulatory diseases

(A 6) A statistically significant association between CD mortality and radiation exposure was observed among male radiation workers of British Nuclear Fuels plc (BNFL) (McGeoghegan et al., 2008). Although part of this cohort consisted of uranium workers (37% of the cohort was employed at Springfields uranium processing installation and 6.8% at Capernhurst uranium enrichment installation) and plutonium workers (50.5% of the cohort was employed at the Sellafield reprocessing installation), no formal study of the effects of uranium or plutonium on the circulatory system has been performed to date. However, the CD mortality ERR/Sv associated with external exposure to gamma radiation was less for those monitored for exposure to internally deposited radionuclides than that for workers not so-monitored.

(A 7) One cohort study suggested an increasing CD mortality risk related to insoluble uranium exposure in France (Guseva-Canu et al., 2012). The cohort considered 2897 workers employed at the AREVA NC Pierrelatte uranium processing plant between 1960 and 2006 (79,892 person-years). Cumulative exposure to different uranium compounds, classified by isotopic composition and solubility-type, was assessed using a plant-specific job-exposure-matrix. Hazard ratios and associated 95% confidence intervals (HR [95%CI]) were estimated using Cox regression models accounting for sex, calendar period, initial socioeconomic status and associated exposure. The number of CD deaths was 111 including 48 from ischemic origins and 31 from CeVD. Cardiovascular mortality risk appeared increased among workers exposed to insoluble compounds of reprocessed uranium (HR=2.07 [0.99-4.99], n=9), but this result was based on a limited number of workers.

(A 8) A nested case-control study has been performed in French AREVA NC Pierrelatte nuclear workers employed between 1960 and 2005 to estimate CD risks adjusting for major CD risk factors (smoking, blood pressure, body mass index, total cholesterol and glycaemia) and external γ-radiation dose (Zhivin et al., 2018). The study included 102 cases of death from CD and 416 controls individually matched on age, gender, birth cohort and socio-professional status. Information on CD risk factors was collected from occupational medical records. Organ-specific absorbed doses were estimated using biomonitoring data, taking into account exposure regime and uranium physicochemical properties. External gamma radiation was measured by individual dosimeter badges. Workers were exposed to very low radiation doses (mean gamma-radiation dose of 2 mGy and lung uranium dose of 1 mGy). A positive but imprecise association was observed (excess OR per mGy 0.2, 95% CI 0.004 to 0.5). Results obtained after adjustment suggested that uranium exposure might be an independent CD risk factor. The authors concluded that a positive association might exist between internal uranium exposure and CD

mortality, not confounded by CD risk factors, but caution should be exercised in interpreting the results due to numerous uncertainties associated with internal uranium dose estimation.

A.3. Conclusion

(A 9) Some results are suggestive of an association between plutonium or uranium exposure and an increased risk of CD. In particular, some results from the Mayak worker cohort suggest an association between plutonium exposure and risk of both cerebrovascular diseases and ischemic heart diseases. Nevertheless, the results are based on a small number of studies and some discrepancies and inconsistencies persist, between and within cohorts, and between incidence and mortality data. Extension of these studies in the future is needed, as well as verification of the repetition of such results in other populations.

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GLOSSARY

Absorbed dose, D

The absorbed dose is given by

$$D = \frac{\mathrm{d}\bar{\varepsilon}}{\mathrm{d}m}$$

where $\mathrm{d}\bar{\varepsilon}$ is the mean energy imparted by ionising radiation to matter of mass dm. The SI unit of absorbed dose is joule per kilogram (J kg^{-1}), and its special name is gray (Gy).

Absorption

Transfer of material to blood regardless of mechanism. Generally applies to dissociation of particles and the uptake into blood of soluble substances and material dissociated from particles.

Activity

see radioactivity.

Aerodynamic diameter (d_{ae})

Diameter of a unit density (1 g cm^{-3}) sphere that has the same terminal settling velocity in air as the particle of interest.

Alimentary tract

All structures, largely tubular, from mouth to anus in which ingested material is transported and/or digested and possibly absorbed into the circulatory system.

Alveolar-interstitial (AI) region

The distal part of the respiratory tract, consisting of the respiratory bronchioles, alveolar ducts and sacs with their alveoli, and the interstitial connective tissue; i.e. the airway generations 16 or beyond.

Activity median aerodynamic diameter (AMAD)

Fifty percent of the activity in the aerosol is associated with particles of aerodynamic diameter (d_{ae}) greater than the AMAD. Used when deposition depends principally on inertial impaction and sedimentation, typically when the AMAD is greater than about 0.3 μm.

Basal cells

Cuboidal epithelial cells attached to the basement membrane of epithelial structure typically found at the deepest layer of skin, internal cavity or duct like alimentary tract or airways in the lungs.

Becquerel (Bq)

The special name for the SI unit of activity; 1 Bq = 1 s^{-1}.

Bioassay

Any procedure used to determine the nature, activity, location or retention of radionuclides in the body by direct (*in-vivo*) measurement or by indirect (*in-vitro*) analysis of material excreted or otherwise removed from the body.

Bone marrow.

Bone marrow, a semi-solid tissue located within the spongious portions of bones, is the primary site of new blood cell production or hematopoiesis. It is composed of hematopoietic cells, marrow adipose tissue, and supportive stromal cells. A newborn baby's bones exclusively contain hematopoietically active 'red' marrow, and there is a progressive conversion towards inactive 'yellow' marrow with age. In adult humans, active bone marrow is primarily located in the ribs, vertebrae, sternum, and bones of the pelvis.

Bronchial region (BB)

Part of the respiratory tract, consisting of the trachea (airway generation 0) and bronchi, airway generations 1 through 8.

Bronchiolar region (bb)

Part of the respiratory tract, consisting of the bronchioles and terminal bronchioles; airway generations 9 through 15.

Case-control study

Type of epidemiological study in which a group of subjects with the disease of interest (e.g. cases with lung cancer) is compared with a group of subjects who are free of this disease (controls) but have similar characteristics (sex, attained age, etc.).

A nested case–control study is a specific type of case–control study, in which both cases and controls are extracted from a cohort study, aiming to obtain a more detailed evaluation than possible within the entire cohort.

Cohort study

Type of epidemiological study in which a population exposed to different levels of radionuclides is followed over time for the occurrence of diseases (including lung cancer). This type of epidemiological design was most often used in workers studies. The exposure in time was considered for each individual on an annual basis.

DDREF

A judged factor that reflects the hypothesis of a lower biological effectiveness (per unit of dose) of radiation exposures at low doses and low dose rates as compared with exposures at high doses and high dose rates.

Deposition

Refers to the initial processes determining how much of the material in the inspired air remains behind in the respiratory tract after exhalation. Deposition of material occurs during both inspiration and exhalation.

Detriment

A concept used to quantify the total harmful stochastic health effects experienced by an exposed group and its descendants as a result of the group's exposure to radiation. Detriment is an integrated multi-dimensional concept. Its principal components are the stochastic quantities: sex and population average lifetime risk of cancer and probability of heritable effect, and weights to express the severity of the harm(s), such as lethality and length of life lost if the harm occurs.

Effective dose, E

In accordance with the generic definition of effective dose in *Publication 103*, the effective dose is calculated as:

$$E = \sum_T w_T \left[\frac{H_T{}^M + H_T{}^F}{2} \right]$$

where $H_T{}^M$ and $H_T{}^F$ are the equivalent doses to the tissues or organs r_T of the Reference Adult Male and Female, respectively, and w_T is the tissue weighting factor for target tissue T, with $\sum_T w_T = 1$. The sum is performed over all organs and tissues of the human body considered to be sensitive to the induction of stochastic effects. Since w_R and w_T are dimensionless, the SI unit for effective dose is the same as for absorbed dose, J kg^{-1}, and its special name is sievert (Sv).

Endosteum (or endosteal layer)

A 50 µm-thick layer covering the surfaces of the bone trabeculae in regions of trabecular spongiosa and those of the cortical surfaces of the medullary cavities within the shafts of all long bones. It is assumed to be the target region for radiogenic bone cancer. This target region replaces that previously introduced in *Publications 26* and *30* (ICRP, 1977, 1979) – the bone surfaces – which had been defined as a single-cell layer, 10 µm in thickness, covering the surfaces of both the bone trabeculae and the Haversian canals of cortical bone.

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Equivalent dose, H_T

The equivalent dose to an organ or tissue is given by:

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

where w_R is the radiation weighting factor for radiation R and $D_{R,T}$ is the mean absorbed dose from radiation R in a tissue or organ T. The SI unit for equivalent dose is joule per kilogram (J/kg^{-1}), and its special name is sievert (Sv).

Gray (Gy)

The special name for the SI unit of absorbed dose; 1 Gy = 1 J kg^{-1}.

Human alimentary tract model (HATM)

Biokinetic model for describing the movement of ingested materials through the human alimentary tract; published in *Publication 100* (ICRP, 2006).

ICRP, 2006. Human alimentary tract model for radiological protection. ICRP Publication 100, Ann. ICRP 36 (1-2).

Human respiratory tract model (HRTM)

Biokinetic model for describing the deposition, translocation and absorption of inhaled materials in the human respiratory tract; published in *Publication 66* (ICRP, 1994) and updated in *Publication 130* (ICRP, 2015).

ICRP, 1994. Human respiratory tract model for radiological protection. ICRP Publication 66, Ann. ICRP 24(1-3).

ICRP, 2015. Occupational Intakes of Radionuclides: Part 1. ICRP Publication 130. Ann. ICRP 44(2).

Intake. See also ‘Uptake’

Radionuclide that enters the respiratory tract or gastrointestinal tract from the environment. Acute intake is defined as a single intake by inhalation or ingestion, taken to occur instantaneously; and chronic intake is defined as a protracted intake over a specified period of time.

Particle transport

Processes that clear material from the respiratory tract to the alimentary tract and to the lymph nodes, and move material from one part of the respiratory tract to another.

Potential alpha energy concentration (PAEC)

The concentration of short-lived radon or thoron progeny in air in terms of the alpha energy emitted during complete decay from radon-222 progeny to lead-210, or from radon-220 progeny to lead-208, of any mixture of short-lived radon-222 or radon-220 in a unit volume of air.

Radiation weighting factor, w_R

A dimensionless factor by which the organ or tissue absorbed dose component of a radiation type R is multiplied to reflect the relative biological effectiveness of that radiation type. It is used to derive the organ equivalent dose from the mean absorbed dose in an organ or tissue.

Radioactivity

The property of an unstable atomic nucleus losing energy by emitting radiation (radioactive decay). Radioactivity also refers to the expectation value of the number of radioactive decays occurring in a given quantity of material per unit time. The SI unit of radioactivity is per second (s^{-1}) and its special name is becquerel (Bq).

Radon progeny

The decay products of radon-222, used in this report in the more limited sense of the short-lived decay products from polonium-218 to polonium-214. Radon progeny are sometimes referred to as 'radon decay products'.

Reference biokinetic model

A biokinetic model adopted in this report series for the Reference Worker. A reference biokinetic model describes the intake, uptake, distribution, and retention of a radionuclide in various organs or tissues of the body and the subsequent excretion from the body by various pathways.

Reference Worker

An adult Reference Person combined with the reference biokinetic and dosimetric models and their parameter values, as defined in this report series for the Reference Worker (systemic biokinetic models, HRTM, HATM, and dosimetric models). The structure and parameter values of biokinetic models of the Reference Worker are invariant on the sex, age, race and other individual-specific characteristics, but based on Reference Male parameter values where sex-specific models are available.

Risk

Risk relates to the probability or chance that an outcome (e.g. lung cancer) will occur. Terms relating to risk are listed below:

Excess absolute risk: An expression of risk based on the assumption that the excess risk from radiation exposure adds to the underlying (baseline) risk by an increment dependent on dose but independent of the beseline rate.

Excess relative risk: The rate of disease in an exposed population divided by the rate of disease in an unexposed population, minus 1. When studying a dose–response relationship, this is expressed as the excess relative risk per Gy or per Sv: (Relative risk - 1)/unit of exposure.

Relative risk: The ratio of the incidence rate or the mortality rate from the disease of interest (e.g. lung cancer) in an exposed population to that in an unexposed population.

Risk coefficient: Increase of risk per unit exposure or per unit dose. In general, expressed as excess relative risk per Bq, or per Sv.

Risk model: A model describing the variation of the risk coefficient as a function of modifying factors, such as time since exposure, attained age, or age at exposure. It may be related by a factor to the age-specific baseline risk (multiplicative) or added to the baseline risk (additive).

Lifetime risk: Risk cumulated by an individual up to a given age.Lifetime risk is often expressed as the number of cases of a disease arising per 10,000 individuals over lifetime. The estimate used in the present report is the lifetime excess absolute risk associated with an exposure scenario, expressed in number of deaths per 10,000 person-years per Gy (also sometimes denominated as the radiation excess induced death). In the present report, unless otherwise stated, the lifetime age is 90 years as generally considered by the Commission.

Secretory cells

Nonciliated epithelial cells that have mucous or serous secretions.

Sievert (Sv)

The special name for the SI unit (J kg^{-1}) of equivalent dose and effective dose.

Tissue weighting factor, w_T

The factor by which the equivalent dose in a tissue or organ T is weighted to represent the relative contribution of that tissue or organ to the total radiation detriment resulting from uniform irradiation of the body. It is weighted such that:

$$\sum_T w_T = 1$$

Uptake. See also 'Intake'

Activity that enters blood from the respiratory or alimentary tract or through the skin.

Working level (WL)

Any combination of the short-lived progeny of radon in one litre of air that will result in the emission of 1.3 x 10^5 MeV of potential alpha energy. 1 WL = 2.08 10^{-5} J m^{-3}.

Working Level Month (WLM)

The cumulative exposure from breathing an atmosphere at a concentration of 1 working level for a working month of 170 h.

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W. E. Bolch	N. Ishigure	A. S. Pradhan

(2013–2017)

J.D. Harrison (Chair)	M. Degteva	D. Noβke
M. R. Bailey	A. Endo	F. Paquet
V. Berkovskyy	N. Petoussi-Henss	N. Petoussi-Henss
L. Bertelli	C. Hyeong Kim	F. Wissmann
W. E. Bolch	R. Leggett	
D. Chambers	J. Ma	

(2017-2021)

J.D. Harrison (Chair)	F. Paquet (Vice-Chair)	W.E. Bolch (Secretary)
V. Berkovskyy	E. Blanchardon	A. Giussani
D. Jokisch	C.H. Kim	R.W. Leggett
J. Li	M.A. Lopez	N. Petoussi-Henss
T. Sato	T. Smith	A. Ulanowski
F. Wissmann		