SOURCES, EFFECTS AND RISKS OF IONIZING RADIATION

United Nations Scientific Committee on the Effects of Atomic Radiation

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NOTE

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Sources, Effects and Risks of Ionizing Radiation: UNSCEAR 2016 Report to the General Assembly, Scientific Annexes A, B, C and D

Corrigendum

Annex D, page 438, paragraph 319, last line

should read

(18.6 mBq/d) and not (18.6 mBq/L)

V.18-03158

ANNEX D

BIOLOGICAL EFFECTS OF SELECTED INTERNAL EMITTERS—URANIUM

CONTENTS

I. INTRODUCTION

1. This annex provides a review of the scientific literature on characteristics of uranium, its biokinetics and dosimetry within the human body for various physical and chemical forms and routes of intake into the body, radiobiological and toxicological effects of exposure to uranium, and epidemiological studies of nuclear workers and the public who have been exposed to uranium.

2. Uranium was discovered by Martin Heinrich Klaproth in 1789 and its radioactive properties by Antoine Henri Becquerel in 1896. Uranium, element 92 in the periodic table, is present naturally in all rock and soil. Levels of uranium content in soil depend on local geology and range widely from a few mg/kg up to levels of several per cent in ore bodies. The Committee in its UNSCEAR 2008 Report [U10] reported a median activity concentration of around 30 Bq/kg (1.2 mg/kg) for uranium in rock and soil. Uranium is released to the environment through natural events such as forest fires and volcanoes and released from rock and soil through natural processes. It is distributed through mechanisms such as leaching to ground and surface water and through wind erosion of soil. In turn, uranium in water, soil and air is taken up by plants and animals. People may be exposed to uranium by inhalation of airborne particulates, through skin uptake and through ingestion of uranium in food and water.

3. There are three naturally-occurring, alpha-particle emitting, isotopes of uranium: ^{238}U, ^{234}U and ^{235}U. Two of these, ^{238}U and ^{235}U, with radioactive half-lives of 4.47×10^9 and 7.04×10^8 years respectively, are the parents of radioactive decay chains that are major contributors to the background radiation exposure of the human population. Uranium-238 supports 14 decay products. The isotope ^{234}U, with a half-life of 2.45×10^5 years, is a member of the ^{238}U decay chain. In natural uranium, ^{238}U is the most abundant isotope in terms of mass (99.2742%), while ^{234}U and ^{235}U constitute only 0.0054% and 0.7204%, respectively [N8, S15]. Figure I shows a simplified radioactive decay chains for ^{238}U. Other isotopes, such as ^{232}U, may be produced in thorium breeder reactors. Further, ^{236}Uranium, with a half-life 2.35×10^7 years, is present in spent nuclear fuel and in reprocessed uranium [W24], and occurs naturally as a very small component of natural uranium ($<10^{-11}$% by mass).

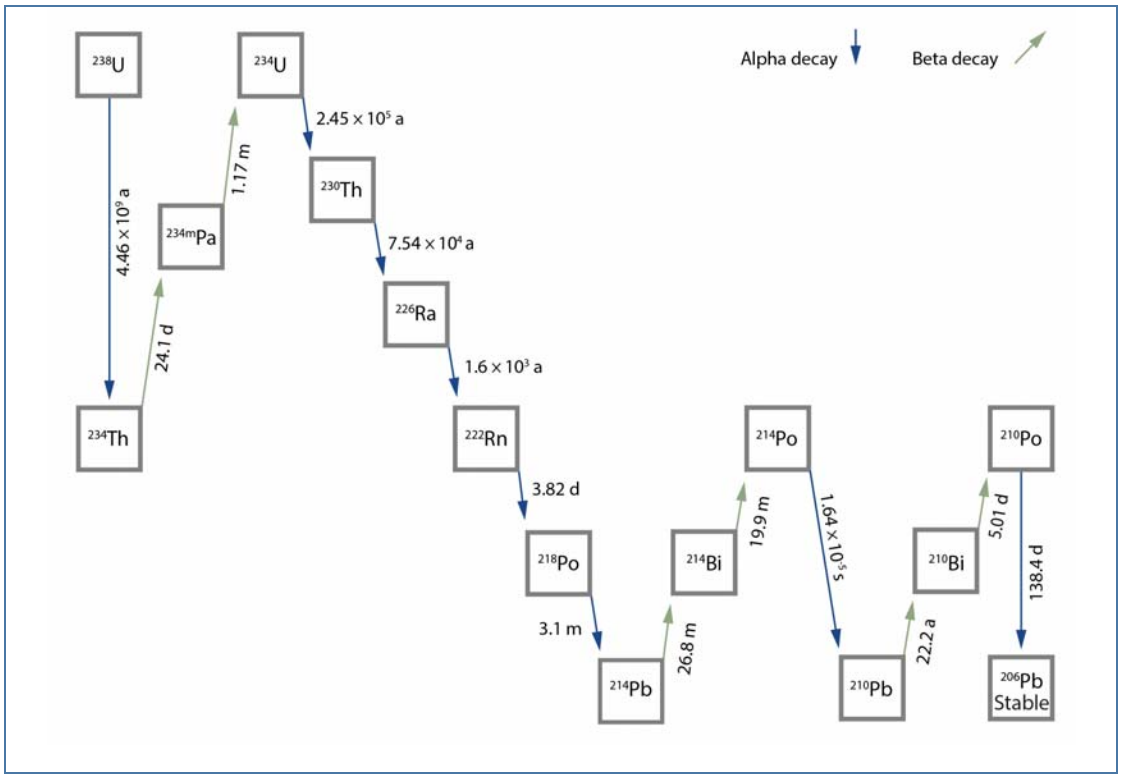
4. Both ^{238}U and ^{234}U, when in secular equilibrium, contribute 48.9% of the total alpha particle activity of natural uranium, while ^{235}U contributes 2.2%. Some nuclear reactors require fuel that is enriched to the fissionable isotope ^{235}U. Current technologies for enriching natural uranium are gaseous diffusion and centrifugation. Enrichment increases the proportion of ^{235}U from its natural levels (0.72%) to 2–5%, depending on the design requirements of nuclear power reactors. In addition, higher enrichment levels (>90% of ^{235}U) are achieved for use in weapons. The term depleted uranium (DU) refers to isotopic mixtures that contain a lower percentage of ^{235}U than is present in naturally occurring uranium. It is recovered as a by-product of the enrichment process. The proportion of ^{235}U in DU is between 0.2 and 0.3%. Reprocessed uranium (especially from earlier military reprocessing) may also be contaminated with traces of fission products and transuranic elements [W24].

5. Uranium compounds exhibit differences in their chemical and physical properties and, as a result, also differ in their toxicological properties. For example, uranium compounds vary widely in their solubility and this can result in differences in bioavailability following intake (via inhalation or ingestion) into the body [A31, L9, S37, U16]. The biological and health effects of uranium are due to its chemical and radiological toxicity. In general, this toxicity, as demonstrated in animal studies, is caused by chemical rather than radiological components, excepting that effects induced by the isotopes of higher specific activity and by enriched uranium are more probably due to radiation exposure.

6. Since 1949, many animal studies have indicated that the toxicity of uranium is due mainly to chemical damage to the kidneys [A25]. Other systems or organs may also be affected by exposure to uranium, such as the skeleton [A26], the lungs [L18], the gonads [A19] and the liver [P6].

Figure I. Radioactive decay chain for ^{238}U [I17]

Half-life is expressed in a = year; d = day; h = hours; m = minutes; s = seconds



7. Uranium concentrations in environmental media may be measured in terms of radioactivity (measured in Bq/L, e.g. by alpha spectrometry) or mass (measured in µg/L, e.g. by high-resolution inductively coupled plasma mass spectrometry). Consequently, data on uranium levels in soil, air, water and food are indicated in Bq/L and in µg/L.

8. A general concept is the relation between radioactivity and mass. As mentioned above, the *activity* of each member of a chain headed by a parent radionuclide would be the same under conditions of secular equilibrium, but the *mass* of each member of the chain would be quite different. The relationship between activity, A, and mass, M, of a radionuclide is given by:

$$A = \frac{A_0 \times \lambda}{AW} \times M = \frac{A_0}{AW} \times \frac{Ln(2)}{T_{1/2}} \times M$$

where

A = activity of a radionuclide, Bq;
A_0 = Avogadro's constant, 6.023×10^{23} atoms/mole;
AW = atomic weight of the radionuclide, kg/mole;
λ = decay constant, dis/(atom s);
$T_{1/2}$ = half-life of the radionuclide, s;
M = mass of the radionuclide, kg.

For natural uranium, the activity is 25,400 Bq/g (table 1). However, as shown in table 1, the natural relative abundance of ^{234}U, ^{235}U and ^{238}U can be expressed in terms of either numbers of atoms or weight, giving slightly different values [K3, M31, M32].

Table 1. Mass activities of the three natural isotopes of uranium [K3]

Natural uranium	*Relative abundance*	
	atoms% (wt%)	*mBq/μg U*
^{238}U	99.274 (99.284)	12.40
^{235}U	0.720 (0.711)	0.60
^{234}U	0.0054 (0.0053)	12.40

II. SOURCES AND LEVELS

A. Natural sources

1. Levels in soil

9. Naturally occurring radionuclides in the environment affect the levels of background radiation encountered at different locations around the world [N2, U8]. As mentioned by Cuney [C38], three types of deposits contain more than three quarters of the worldwide uranium resources: unconformity-related deposits, iron oxide–copper–gold (IOCG) deposits, and sandstone-hosted deposits [L10].

10. The concentration of uranium in soil varies with location and local geology. Its concentration is relatively low in basic rock, such as basalt, and higher in acid rock, such as the sedimentary rock saturated with silica. The uranium content of granites is higher still [U10]. For example, the nominal activity concentration of uranium in soil is about 15 Bq/kg of ^{238}U (1.2 mg/kg) with a typical activity range of 10–50 Bq/kg (0.4 to 2 mg/kg) [N2, U10]. Much higher concentrations are found in uranium mining areas such as the Northern Saskatchewan in Canada, the Colorado Plateau and central Florida where phosphate is mined. The uranium content of phosphate rock used for phosphate fertilizers ranges from about 50 to 2,400 Bq/kg of ^{238}U (4–190 mg/kg) [A31, N2, R20, U8]. One of the highest activity concentrations worldwide is localized in the region of Recife in Brazil, with sedimentary rock that contains 30–500 mg/kg with an average of 150 mg/kg (1,860 (range 372–6,200 Bq/kg of ^{238}U)) [S18]. However, since uranium in soil may be more or less tightly bound depending on soil characteristics, the uranium speciation in soil has an impact on bioaccessibility in the gut.

2. Levels in air

11. Soil particles containing uranium may be transferred into the atmosphere through natural mechanisms. The natural uranium concentration in air is typically very low, varying from location to location according to local ground sources [H19]. Airborne uranium can deposit on soil, plants and open water as dry or wet deposition [A31].

12. Golchert et al. [G16] measured airborne concentrations of ^{238}U of around 0.3 μBq/m^3 at a site near the Argonne National Laboratory (Illinois, United States). Average levels of natural uranium in ambient air have been reported to be 0.25 μBq/m^3 of ^{238}U (0.02 ng/m^3) in Tokyo [H19]. Tracy and Prantl [T17] found the average concentration of ^{238}U in air in a southern Ontario rural environment to be about 1.25 μBq/m^3 (0.1 ng/m^3), on the basis of measurements of ^{226}Ra in dust and an assumption of equilibrium between ^{238}U and ^{226}Ra. Taken together, these different values indicate an average uranium level in air of around 1 μBq/m^3.

13. The World Health Organization (WHO) [W14] estimates that an adult of average size inhales 20 m^3 of air per day with a nominal natural uranium concentration of 0.6 μBq/m^3 of ^{238}U (0.05 ng/m^3), corresponding to 12.4 μBq (1 ng) of ^{238}U. These values lead to a calculated annual intake through inhalation by adults of approximately 0.0045 Bq of ^{238}U. For comparison, tobacco smoke (from two packages of cigarettes per day) contributes to 0.11 Bq of ^{238}U (corresponding to 9 μg) of inhaled natural uranium per year [L49].

3. Levels in water

14. As long as uranium is inside undisturbed crystalline rock in secular equilibrium with its progeny, the ratio of ^{234}U to ^{238}U is expected to be one. Nevertheless, disequilibrium can be observed when rock is disturbed by chemical or physical processes involving water. As a result, water from any source may contain ^{234}U/^{238}U ratios greater than unity because of the greater mobility and increased availability of ^{234}U, generally due to a reducing environment [D1]. Two isotopes in the decay series, ^{234}Th and ^{234m}Pa, separate the two uranium isotopes and their different solubilities in the source rock, permitting ^{234}U to be released preferentially and leading to variations in the ratio ^{234}U/^{238}U [O9]. In addition, the total uranium activity present in water may influence the ^{234}U/^{238}U ratio. Indeed, Ortega et al. found that ~80% of samples with a high ratio of disequilibrium (>1.6) were linked to the lowest uranium activities <50 mBq/L, when the samples with a low activity ratio (<1.5) corresponded to samples with high concentrations of uranium (>200 mBq/L) [O8].

15. Uranium is present in different water sources (surface water, groundwater and drilled water) at variable levels [W16]. In oxygenated surface water, uranium levels were found at around 0.02 to 6 μg/L (0.25–76 mBq/L of ^{238}U). In sea water, its average content is 3.3 μg/L (42 mBq/L of ^{238}U), often bound by ligands or associated with suspended particles [B42]. Natural uranium levels were found to be higher in Precambrian rock aquifers (average, 115.6 μg/L (1.45 Bq/L of ^{238}U)) than in Palaeozoic sedimentary rock aquifers (average, 3.5 μg/L (0.045 Bq/L of ^{238}U)). Cothern and Lappenbusch [C34] reviewed the available data on the occurrence of uranium in surface and groundwater supplies in the United States and reported that surface water samples derived from about 35,000 sources had an average uranium concentration of 18 mBq/L of ^{238}U (1.45 μg/L) (range from 0.18 to about 12,500 mBq/L of ^{238}U (0.014–982 μg/L) and that about 55,000 samples of groundwater supplies had an average uranium concentration of 55 mBq/L of ^{238}U (4.4 μg/L) (range −0.018–12,000 mBq/L of ^{238}U (0.0014–942 μg/L)).

16. The WHO indicated values for uranium levels in water generally less than 12.4 mBq/L of ^{238}U (<1 μg/L) [W15, W18]. The Agency for Toxic Substances and Disease Registry (ATSDR) reported an average concentration of 14.4 mBq/L of ^{238}U (1.16 μg/L) [A31]. This was much higher than the previously reported value by the Committee in its UNSCEAR 1977 Report 0.54 mBq/L of ^{238}U (0.044 μg/L) [U7]. Thus, it might be more appropriate to report median rather than mean values because of the large variation of uranium concentration in water. The Committee reported a variation of natural uranium concentrations measured in drinking water samples in 16 countries of about eight

orders of magnitude [U10]. A global overview of uranium concentration (μg/L) and activity (mBq/L) is given in appendix A, in table A1 for the values measured in groundwater, in table A2 for the values measured in surface water, in table A3 for the values measured in public water supplies and in table A4 for the values measured in bottled mineral water.

17. In Canada, different surveys aimed to measure uranium levels in drinking water in different provinces. The mean natural uranium concentration in surface water and groundwater (some treated) supplies was about 50 mBq/L of ^{238}U (4 μg/L) in southern-central British Colombia [P32], 124 mBq/L of ^{238}U (10 μg/L) in south-eastern Manitoba [B21], 65 mBq/L of ^{238}U (5.2 μg/L in the Kitigan Zibi First Nation community in Quebec) [M58], and 5 mBq/L of ^{238}U (0.40 μg/L) in Ontario [O3]. In summary, the analysis of the different values measured in these surveys indicates that mean uranium levels in drinking water were extremely variable in the different Canadian counties/provinces, from 5 to 750 mBq/L of ^{238}U (0.4–58.3 μg/L), including great internal variations depending on the precise location. Furthermore, behind these average uranium levels in drinking water, more extreme values were measured in some Canadian provinces or some counties in the United States as indicated in appendix A, table A1. In fact, natural uranium concentrations as high as 8,680 mBq/L of ^{238}U (700 μg/L) were found in private groundwater supplies [M64, M65]. A value of 25,048 mBq/L of ^{238}U (2,020 μg/L) was measured in groundwater in south-eastern Manitoba [B21].

18. Concerning water in the United States, official reports indicated an average natural uranium concentration of 31.6 mBq/L of ^{238}U (2.55 μg/L) in drinking water from 978 sites in the 1980s [U14]. These values are higher than those mentioned in a study by Fisenne et al. with mean activity of natural uranium in drinking water in New York City ranging from 0.62 to 1.25 mBq/L of ^{238}U (0.05 to 0.09 μg/L) [F5]. In this study, New York city tap water had ^{234}U, ^{235}U and ^{238}U activities of 1.04±0.19, 0.035±0.010 and 0.87±0.18 mBq/L, respectively [F5]. Maximum values were measured in Connecticut 86.472 mBq/L of ^{238}U (7,780 μg/L). As for Canada, differences may relate to geographical variations and local geology (appendix A, table A1).

19. In Finland, national and local surveys of uranium content in water distributed by Finnish waterworks have been conducted. The median value was of 1.9 mBq/L of ^{238}U (0.15 μg/L) [T22] (appendix A, table A1). An extreme value of 114,100 mBq/L of ^{238}U (9,200 μg/L) was measured in the South of Finland [M66]. It is noteworthy that although the uranium concentrations in Finnish wells drilled in bedrock are among the highest in the world [K26, M66, M67, P28], the uranium concentration in water distributed by the waterworks is generally low [M67, T22].

20. In France, periodic reports address the levels of the radiological quality of drinking water [I21]. Measurements performed during 2008 and 2009 indicate that ^{226}Ra and uranium isotopes constitute the main contributors to a total alpha activity above 0.1 Bq/L; in this case, the mean value of uranium concentration was 2.22 μg/L (27.5 mBq/L of ^{238}U) with a range from 0.14 to 114 μg/L (1.8-1,450 mBq/L of ^{238}U) [I21].

21. Activity concentrations of natural radionuclides in soil, food, natural and drinking water were also measured in China [P2]. However, measurements of uranium were not reported for food and drinking water. Except for salt water lakes that presented higher uranium levels (22 μg/L or 272.5 mBq/L of ^{238}U), the values for uranium in freshwater lakes, reservoirs, rivers, hot and cold springs, well water and sea water were similar (2.2 μg/L with a range from 0.87 to 3.82 (27.3 mBq/L of ^{238}U with a range from 10.78 to 47.3 mBq/L of ^{238}U).

22. The guidance levels of radionuclide concentration provided in the WHO Guidelines for Drinking-Water Quality are based on an individual dose criterion (IDC) of 0.1 mSv committed effective dose from one year's consumption of drinking water. They are expressed as activity concentration for a

given isotope (Bq/L) and were calculated by dividing the IDC of 0.1 mSv per year by the product of the isotope dose conversion factor (Sv/Bq) and an assumed water consumption of 2 L per day (i.e. 730 L per year). The guidance levels of radioactivity concentration for ^{238}U and ^{234}U have been rounded to 10 Bq/L and 1 Bq/L, respectively [W18].

23. Due to the fact that the uranium chemical toxicity is generally of greater importance than radiological effects, several national and international guidelines refer to concentrations of uranium in drinking water, as indicated in table 2. Guideline values (in mg/L or µg/L) were derived from the total tolerable daily intake (TDI) expressed in mg/kg or µg/kg of body weight (e.g. 60 kg for an adult used by WHO), itself based on the no observed adverse effect level (NOAEL)[1] or lowest observed adverse effect level (LOAEL) for kidney toxicity, divided by an uncertainty factor of 100 (for intra- and interspecies variation), and taking the daily drinking water consumption into account (~2 litres) [W16].

Table 2. National and international guidelines for uranium content in drinking water

Only chemical aspects of uranium toxicity are addressed in these guidelines

Organizations/countries	*Uranium in drinking water (µg/L)*	*Reference*
Australia	17	[N5]
Bulgaria	60	[E2]
Canada	20	[H16]
Finland	100	[E2]
Germany	10	[B27]
Slovenia	6.8	[E2]
USA	30	[U17]
WHO	30	[W18]

24. The WHO chemical guideline value for uranium in drinking water significantly increased from 2 µg/L in 1998 up to 15 µg/L in 2004 and then to 30 µg/L in 2011 [W18]. The current WHO chemical guideline of 30 µg/L is still designated as provisional because of scientific uncertainties regarding uranium toxicity, notably with regard to possible carcinogenic effects of uranium [A17] and specific sensitivity of some groups, such as children or people with hypertension or osteoporosis [F15].

25. Tables A1–A4 in appendix A show that uranium concentrations may exceed guideline values in several countries, including those of water from public supplies. In a study of 476 Norwegian groundwater samples, 18% had natural uranium concentrations in excess of 20 µg/L (0.25 Bq/L of ^{238}U) [F12]. Natural uranium concentrations in groundwater in excess of 20 µg/L (0.25 Bq/L) have also been reported in parts of New Mexico, the United States [H5], central Australia [F9] and France [I21]. Some Finnish studies noted a median uranium concentration of 28 µg/L (0.35 Bq/L of ^{238}U) and 285 µg/L (3.5 Bq/L of ^{238}U) in drinking water [K26, P28], respectively. In Canada, one study also reported high levels of uranium concentration up to 845 µg/L (10.5 Bq/L of ^{238}U) in private wells [Z8].

26. In a Canadian study, Zamora et al. [Z6] found that water contributed 31–98% of the total daily intake of uranium from food and water for individuals whose drinking water contained uranium at concentrations ranging from 2 to 780 µg/L (25 to 10,000 mBq/L of ^{238}U). This was similar to values

[1] NOAEL: the greatest concentration or amount of a substance that causes no detectable adverse alteration in morphology, functional capacity, growth, or life span of the target organism under defined conditions of exposure [W13].

obtained in studies by the United States Environmental Protection Agency, which reported that uranium in drinking water contributed about 31% [U13, U14] of the total daily uranium intake.

27. In summary, uranium average levels in water worldwide are: 2 µg/L (15 mBq/L of ^{238}U) for groundwater (appendix A, table A1), 1 µg/L (12.4 mBq/L of ^{238}U) for surface water (appendix A, table A2), 1 µg/L (12.4 mBq/L of ^{238}U) for public water supplies (appendix A, table A3), 0.5 µg/L (6.5 mBq/L of ^{238}U) for bottled mineral water (appendix A, table A4) (for natural uranium of 25,400 Bq/g). These median values hide great variability, notably for groundwater (0.0005–7.780 µg/L (0.0063–96,472 mBq/L of ^{238}U)). However, overall only a small proportion of few drinking water samples (generally <3%) exceed the national or international guidelines. As expected, the values for uranium content in bottled mineral water are not so scattered.

4. Levels in food

28. The measurement of the bioaccumulation of uranium in animals and plants shows that concentration factors are dependent on organism characteristics (e.g. species, life stage, physiology), exposure pathways, and the chemical and physical characteristics of the environment [G4, Q2]. Various publications have reported that the most available forms of uranium in plants were phosphate, carbonate, sulphate or citrate forms [L14, L15].

29. Most available data relate to transfer through plants from their roots and the direct contamination of aquatic organisms. Within plants, uranium concentrates mainly in the roots. Uranium found in meat and dairy products results from livestock feeding on plants and on food supplement made from natural phosphates and supplied to dairy cows. Ingestion of soil particles, either directly or through consumption of grass contaminated with soil, is likely to be a significant component of the total intake by livestock. Transfer parameters of natural uranium are known for the main meat-producing species (cattle, sheep and pigs) and also for cow's milk [I1]. They vary between 3.9×10^{-4} and 7.5×10^{-1} day/L in bovine meat and poultry, respectively.

30. Uranium has been detected in a variety of foodstuffs, with great variability. The ^{238}U activity has been estimated to be 100-fold higher in root vegetables than in fruit or leafy vegetables as shown, for example, by measurements for beets and tomatoes (100 vs. 1.13 mBq/kg, respectively) [I2]. A synopsis of the activity of ^{238}U measured by different authors in several types of foodstuffs is contained in the Committee's 1977 Report and in its 2000 Report [U7, U8]. Meat products have the lowest uranium activity (between 0.08 and 20 of ^{238}U mBq/kg). A recent report indicated activities of ^{238}U between 1 and 49 mBq/kg for meat products [R11].

31. An estimate of daily uranium ingestion of food was made in Japan for urban residents [K30]. Concentration of ^{238}U varied between 9.9×10^{-5} and 5.9 Bq/kg depending on food types: grain vinegar and boiled and dried hijiki (a brown sea vegetable), respectively. When prepared diets were analysed, the uranium concentrations observed were, on average, about four times higher than those seen in raw foodstuffs. Hamilton explained this to the possible addition of uranium in seasonings and to transfer from the cookware [H8]. It was unclear whether these dietary intakes included those from drinking water and it was emphasized that the latter had sometimes been found to be equal to that from the diet [H8]. Wrenn et al. have suggested that in regions where treated surface water was used for cooking and drinking, food appeared to be the major source of uranium intake [W26].

32. In aquatic animals (crustaceans, molluscs and fish), the bioconcentration factor from water is very low [I3]. Concentration factors for fish vary from 0.01 to 20. The values depend on the behaviour of the organisms (pelagic species accumulate approximately 10 times less than benthic species) and the

tissues considered (bone 200–8,000 and kidneys > liver and gills > muscles 1.5–24 > digestive system > gonads). A study was performed in Japan to determine uranium concentrations in marine organisms (soft tissues) [M15]. This study showed large differences in uranium levels depending on the marine species, with a minimum value of 0.077 μg/kg (0.97 mBq/kg of ^{238}U) measured in rockfish (kichiji) and a value of 5,040 μg/kg (63.8 Bq/kg of ^{238}U) found in octopus. The values reported by Belles et al. also indicated that fish and seafood showed the highest uranium concentrations (90 μg/kg, 1.1 Bq/kg of ^{238}U), followed by dairy products (40 μg/kg, 0.5 Bq/kg of ^{238}U) [B12].

33. The concentrations of uranium in fish are also dependent on uranium levels in water. The uranium concentrations in the muscle (dry weight) of fish caught in a Canadian lake receiving effluents from a uranium mill were 7–11 times higher than those from fish caught in uncontaminated lakes [S50]. Uranium mines and mills operating between the 1940s and the late 1970s have left behind legacy contamination due to historic mining and milling practices and incomplete site remediation during decommissioning. In Beaverlodge Lake, Northern Saskatchewan, Canada, elevated concentrations of uranium are still present with a mean concentration for the period 2013–2015 of approximately 135 μg/L (range 130–142) corresponding to 1.69 Bq/L of ^{238}U (range 1.63–1.78) [C2, C3, C4].

34. Human health risk assessments for environmental contaminants take soil ingestion rates into consideration. The value recommended by Richardson and Stantec Consulting Ltd. [R13] of 20–40 mg/d for children is based on mechanistic assessments made by Wilson et al. [W21] and Ozkaynak et al. [O10]. Another report suggested assessing health risk for children with the value of 100 mg of soil per day [U15]. However, uranium bound to soils is not completely bioavailable. Reported bioaccessibility (in vitro estimate of bioavailability) values are quite variable ranging from 21±12% in the gastric phase and 48±17% in the gastric and intestinal phase [J4] to less than 5% in the gastro-intestinal phase [T16].

35. The urinary concentrations of several metals, including uranium, were found to be higher than international reference values in a study of schoolchildren and working children in Lahore, Pakistan [S44]. The measured urinary concentrations of uranium corresponded well with uranium concentrations in drinking water.

36. A study of 19 categories of food was performed by Fisenne et al. [F5, F6]. Potatoes, meat, fresh fish and bakery products were found to contribute more than 70% of the average uranium intake (1.2 μg/d or 14.9 mBq/d of ^{238}U). Dietary levels of uranium in the United Kingdom were reported in a study of typical diets using both raw and prepared foodstuffs. Analysis of the raw foodstuffs indicated that 83% of the daily intake of uranium derived from starchy roots, vegetables and fruit, and cereals.

37. The Committee in its 1977 Report [U7] included a summary of ^{238}U concentrations in foodstuffs in France, Japan and the former Soviet Union along with the results given above for the United States and the United Kingdom. In areas with typical uranium concentrations in soils, the daily dietary intake fell within a relatively small range, ~0.9 to 1.5 μg natural uranium (11.5 to 19 mBq of ^{238}U). This range is consistent with values given in several publications calculated from the mass activity of natural uranium (25,400 Bq/g): 1.32 μg/day corresponding to 16.4 mBq/day of ^{238}U for typical diets of adults in New York City, Chicago and San Francisco in the United States [W11], 1.14 μg/day (14.5 mBq/day of ^{238}U) [K30] and 1.46 μg (18.6 mBq/day of ^{238}U) in different cities in Japan [N9]. In the United States, the average daily per capita intake of natural uranium in foodstuffs was estimated to range from about 1 to 33 μg (i.e. from about 12 mBq ^{238}U/day to 405 mBq ^{238}U/day) determined from excretion measurements [S26]. The values given by ATSDR indicated that the daily intake of uranium from food sources ranged from 0.9 to 1.5 μg/day [A31, W11]. Similar values were given for European countries [W15]: intakes ranged from 6 to 22 mBq/day of ^{238}U corresponding to 0.47 and 1.77 μg/day, respectively. This daily intake contributed to a body burden of around 50 μg (0.62 Bq of ^{238}U) in humans [F6].

38. The Codex Alimentarius gives guideline levels applied to radionuclides contained in food, destined for human consumption and traded internationally, which has been contaminated following a nuclear or radiological emergency [C29]. These guideline levels apply to food after reconstitution or as prepared for consumption, i.e. not to dried or concentrated foods, and are based on an intervention exemption level of 1 mSv in a year. A value of 100 Bq/kg is given for ^{235}U. However, these guideline levels exclude radionuclides of natural origin such as ^{238}U.

39. In summary, uranium is present in a variety of foodstuffs, with great variability. Potatoes, meat, fresh fish and bakery products were found to contribute more than 70% of the average uranium daily intake. The total daily intake in food was found to be around 1.5 µg (18.6 mBq of ^{238}U), about twice that via drinking water, recognizing that levels in diet and drinking water can vary greatly.

5. Levels in milk

40. Some publications report uranium levels in milk, notably from cattle. The uranium concentrations measured in milk were in a wide range, from 0.012 to 0.41 µg/L (0.15–5.2 mBq/L of ^{238}U), depending on the species and the technical methodology (table 3). A mean value of 0.26 µg/L is given, corresponding to 3.3 mBq/L of ^{238}U (range 0.001–1.20 µg/L; 0.012–15 mBq/L of ^{238}U), if the highest values of Santos et al. [S3] are excluded. This mean value is above the reference value of 1 mBq/L of ^{238}U given in the Committee's UNSCEAR 2000 Report [U8]. Furthermore, transfer coefficients of uranium into milk are also available in the literature [A5, K1, T8, W9, W28] and presented for different species in table 4.

Table 3. Uranium content (mass and activity) in milk (animals)

Values are expressed in kg of fresh matter, the numbers in italics correspond to calculated data obtained from the mass activity of natural uranium of 25,400 Bq/g and from the relative proportion of ^{238}U (12.4 mBq/µg) in natural uranium of 48.3%

[U] in µg/L	*^{238}U in mBq/L*	*Reference*
0.14–0.24	*1.74–2.98*	[A14]
1.20	14.8	[S43]
0.10 (0.03–0.24)	*1.24 (0.38–3.0)*	[F16, M34]
0.72±0.35	8.9±4.3	[A5]
0.001–0.01	0.01–0.12	[R11]
0.21±0.02	2.56±0.25	[P19]
0.25±0.06	3.07±0.74	[P20]
3.09 (0.18–9.6)	38 (2.2–118)	[S3]

Table 4. Transfer coefficients of uranium into milk (animals)

n.i.: not indicated

Species	*Transfer factor (d/L)*	*Range (d/L)*	*Reference*
Cattle	2.0×10^{-4}	6.0×10^{-5}–6.0×10^{-4}	[T8]
Cow	2.9×10^{-3}	5.0×10^{-4}–6.1×10^{-3}	[K1]
Sheep and goat	1.0×10^{-3}	3.0×10^{-4}–3.0×10^{-3}	[T8]
Goat	1.4×10^{-3}	n.i.	[K1]
Camel	4.2×10^{-3}	1.1×10^{-3}–1.5×10^{-2}	[A5]

B. Artificial sources

41. The main application of uranium is for energy production and military use. Uranium-235 is naturally a fissile isotope. Uranium is used primarily in most nuclear power plants. Its utilization in most reactors requires enrichment of natural uranium containing 0.72% by weight of ^{235}U to a ^{235}U content of 2–5%. Weapons use high enriched uranium with over 90% ^{235}U. Some research reactors and naval reactors also use high enriched uranium. Depleted uranium is used as a metal in kinetic energy penetrators and tank armour.

42. The nuclear fuel cycle leading to the production of electricity from uranium in nuclear power reactors includes mining, milling, conversion, enrichment, fabrication of nuclear fuel and reprocessing [G18]. Mining for the extraction of uranium involves both conventional open pit (where deposits are close to the surface) and underground mining (used for deeper deposits). Currently, most uranium mining worldwide uses the in situ leach mining process [S4]. The milling process produces a uranium oxide concentrate, named Yellowcake, which contains more than 80% uranium. This uranium oxide is then converted to uranium hexafluoride (UF_6). It contains only natural uranium, which is enriched via one of the two major types of enrichment technologies, gaseous diffusion or gas centrifuge. The enriched uranium hexafluoride is then converted to uranium dioxide (UO_2) powder and processed into ceramic pellets. Finally, these pellets are inserted into tubes of corrosion-resistant metal alloy, called fuel rods, which are grouped in fuel assemblies for the nuclear fuel core of a power reactor.

43. The uranium remaining after removal of the enriched fraction is DU, containing 0.3% ^{235}U or less [B22, B26]. This uranium has various civilian applications, such as in counterweights or ballast in aircraft or counterweights for rudders and flaps [B22], for X-ray radiation shielding in medical equipment and also for containers for the transport of radioactive material. Moreover, DU has also been used in glassware, ceramics and dentistry.

44. In addition to exposure to natural uranium in the environment, anthropogenic activities have led to increasing uranium exposure for humans. For instance, uranium was found to leach into water from uranium-bearing glass items (maximum uranium in water, 30 µg/L (0.38 Bq/L of ^{238}U) and from ceramic-glazed items in which natural uranium is used as a colouring agent (300 µg/L; 3.7 Bq/L of ^{238}U) [L6].

45. Uranium is present in water as a result of leaching from natural deposits and waste from the mining of uranium and other minerals, releases from the nuclear fuel cycle and the combustion of coal and other fuel [D22, E6, S26, T1]. Phosphate fertilizers, which may contain uranium at concentrations as high as 150 mg/kg, may also contribute to the uranium content of groundwater [S26].

46. Contamination of surface water and groundwater by effluents from uranium mining, milling, and production operations due to in situ leaching methods has been documented [A31, E1, H14, S50]. Table 5 shows some recent data. Except for some specific locations, i.e. at the pit, the values of uranium concentrations in surface water or groundwater are usually below the WHO guideline of 30 μg/L (372 mBq/L of ^{238}U).

47. Since the 1970s, DU is used for kinetic energy penetrators and tank armour, because of its pyrophoricity [B22]. The military applications of DU led to the significant release of this radionuclide into the environment during the conflicts in Iraq and Kuwait (321 tons of DU), in Bosnia-Herzegovina (3 tons of DU), and in the Kosovo (10 tons of DU). More details are given in reports by the United Nations Environment Programme (UNEP) and the National Defence Research Institute (NDRI) [H13, U3, U4, U5, U6].

48. The use of reprocessed DU in mixed oxide (MOX) fuels (constituted by 8–9% of plutonium and ~90% of DU) has been used as a recycling strategy by countries including France and Japan as an option to reduce the necessity for storage of spent fuel [R6].

49. In a study in Tajikistan, uranium concentrations were shown to vary from more than 1,600 μg/L (>20 Bq/L of ^{238}U) at the pit lake to 90 μg/L (1 mBq/L of ^{238}U) in tube supplies and 6.3 μg/L (80 mBq/L of ^{238}U) in drinking water from the neighbouring village [S28]. Another study documented uranium contamination of groundwater in Arizona, the United States after uranium mining [D13]. Approximately 20% of total uranium concentrations in the water samples exceeded the maximum concentration level for drinking water of 0.37 Bq/L of ^{238}U [U17]. In another study, the uranium content was measured in drinking water samples from locations near the uranium mining site at Jaduguda, India [P8] with uranium concentrations between 0.03±0.01 and 11.6±1.3 μg/L – values below the WHO guidelines of 30 μg/L for uranium level in drinking water [W18].

50. Uranium conversion, uranium enrichment and fuel fabrication facilities are other steps in the nuclear fuel cycle, which also release small amounts of uranium to the environment [A31]. Tracy and Meyerhof showed that concentrations of uranium in the air near a uranium refinery were 200 times higher than background concentrations [T18]. For monitoring stations in Port Hope, Canada, where a uranium refinery is operating, the annual average concentration varied between 0.001 and 0.0158 μg/m^3 in 1988 and 1989. Uranium concentrations subsequently decreased and varied between 0.005 and 0.00028 μg/m^3 in the early 2000s [C27]. In 2009, elevated levels of uranium were registered in storage reservoirs of liquid radioactive waste at the Mayak facility, Russian Federation: the concentration was 370 mBq/L to 520 Bq/L for ^{234}U, and 260 mBq/L to 520 Bq/L for ^{238}U [T21].

51. Concentrations of uranium in surface waters downstream from currently operating uranium mines and mills are relatively low and decrease with distance from the point of effluent discharge. For example, between 2000 and 2012 in the vicinity of Canadian uranium mines and mills within 1 km from the discharge points the mean concentration values ranged from 17 to 0.92 μg/L and decreased to mean values in the range of 1.44 to 0.096 μg/L at distances greater than approximately 10 km from discharge points [C28].

52. Environmental contamination by uranium caused by DU in ammunition used in military conflicts was reported in several studies and in UNEP reports [U3, U4, U5, U6]. Uranium in agriculture soil in Kosovo and Bosnia–Herzegovina averaged 1.8 and 3 mg/kg, while concentrations in public drinking water averaged 0.5 μg/L (16.3 mBq/L of ^{238}U) and 0.4 μg/L (5.1 mBq/L of ^{238}U), respectively [C12]. The average uranium concentrations in soil and water were consistent with natural levels, although localized areas of greater concentration were measured in the immediate surroundings of the DU

penetrators [D4, E5, S2]. In the UNEP report on Kosovo, a great variability was observed in uranium concentrations in water samples, with a range between 0.006 and 2.15 μg/L [U4].

53. Carvalho and Oliveira [C12] found high, localized contamination of soil with DU at Djakovica (4,662 Bq/kg of ^{238}U; 376 mg/kg). The water samples collected from public water distribution networks and river water ranged from 0.2 to 0.76 μg/L (2.5–9.7 mBq/L of ^{238}U) and the air samples ranged from 0.8 to 7.2 μBq/m^3. Consistent results from a number of studies indicate that environmental contamination by DU has been very localized and confined to the areas of ammunition impact.

54. Concentrations of uranium were measured in surface and groundwater at the Semipalatinsk nuclear test site, where more than 400 nuclear tests were conducted [L28]. The measurements showed that ^{238}U concentrations in well water within the study area were in the range of 74–213 mBq/L. The results of these studies suggest that diverse human activities involving uranium (from extraction to application) have led to some localized increase of the concentration in the environment.

Table 5. Overview of uranium content in water close to nuclear fuel facilities worldwide

The numbers in italics correspond to calculated data obtained from the mass activity of natural uranium of 25,400 Bq/g and from the relative proportion of ^{238}U (12.4 mBq/µg) in natural uranium (48.3%); * mean value

Country	*Location*	*Type of plants*	*Sample number*	*Total uranium (µg/L)*	*^{238}U (mBq/L)*	*Reference*
Brazil	Lagoa Real	Mining and ore processing	26	5.45 (0.1–259)	*67.6 (1.2–3 212)*	[C13]
Canada	Saskatchewan, Beaverloke Lake	Mining	22	100.8	*1 250*	[Y1]
India	Jaduguda	Mining and ore processing	33	3.2 (0.03–11.6)	39.7 (0.37–144)	[P8]
India	Jharkhand, Narwapahar	Mining	103	0.63 (0.10–3.75)	*7.8 (1.24–46.5)*	[R7]
India	Jharkhand, Bagjata	Mining	10	3.22* (<0.5–11.2)	*40* (<6.2–139)*	[G12]
India	Jharkhand, Banduhurang	Mining	10	2.15* (<0.5–27.5)	*26.7* (<6.2–341)*	[G12]
India	Jharkhand, Bagjata	Mining	40	*(<61–55.9)*	(<12.6–693)	[G13]
Kazakhstan and Kyrgyzstan	Kurdai (Kazakhstan) and Shekaftar, Kavak and Kadji-say (Kyrgyzstan)	Mining	10	28.2 (1.9–35.9) (1 525 in lake at mining pit)	*350 (23.6–445)* *(18 910)*	[U12]
Kyrgyzstan	Mailuu Suu	Mining and milling	25	0.28 (0.27–0.34) (6 820 for tailings)	*3.47 (3.35–4.2)*	[C32]
Nigeria	Jos plateau	Abandoned mining	5	0.10 (0.03–0.27)	*1.24*	[A22]
Nigeria	Abakaliki	Mining	20	2 (0–7)	*24.6 (0–87)*	[O2]
Portugal	Viseu, Quinta do Bispo & Cunha Baixa	Mining	12	*17.7 (1 km)* *0.5 (7 km)*	220 (1 km) 6.2 (7 km)	[C11]
Tajikistan	Taboshar & Digmai	Mining and milling	6	6.95 (3.4–92)	*86.2 (42.2–1 138)*	[S28]
USA	Karnes County, Texas Pana Maria	Mining and milling	6	19.7 (14.8–95)	*244 (183–1 178)*	[M18]
USA	California Juniper		9	3.35 (0.02–52.37)	*42.2 (0.25–649)*	[K8]

III. PHYSICAL, RADIOLOGICAL AND CHEMICAL CHARACTERISTICS

A. Physical and radiological characteristics

55. Uranium is an actinide and has one of the highest atomic numbers (92) of any naturally occurring element. It is a silvery-white metal that is malleable, ductile, slightly paramagnetic, with a very high-density. In its natural state, crustal uranium occurs as a component of several minerals, including carnotite, uraninite (pitchblende) and brannerite, but is not found in the metallic state in nature. In addition, uranium metal is pyrophoric. Due to its pyrophoricity, it is used in military applications, particularly in armor-piercing projectiles.

56. The three naturally occurring isotopes of uranium (^{234}U, ^{235}U and ^{238}U) behave the same way chemically but have different radiological properties (table 6). Uranium-238 has the longest half-life and consequently the lowest specific activity. It is the most abundant naturally occurring uranium isotope. Among the natural isotopes of uranium, ^{234}U has the highest specific activity and the shortest half-life [L35, S15]. However, other isotopes of uranium may be produced, such as ^{233}U that has a very high specific activity (3.57×10^8 Bq/g) [L43].

57. Natural uranium is made of a mixture of the three isotopes described above with about 0.72% of ^{235}U in mass (table 7). Depleted uranium refers to isotope mixtures that contain a lower percentage of ^{235}U (from about 0.2–0.3%) while enriched uranium contains typically 3–5% ^{235}U in mass and may contain up to 90% ^{235}U for military applications (table 7) [L35, S15].

Table 6. Radiological properties of uranium isotopes [N8]

nt: nuclear transformation

Isotope	*Half-life (years)*	*Daughter nuclide*	*Emitted energy (MeV/nt)*			
			Alpha	*Electron*	*Photon*	*Total*
^{234}U	2.46×10^5	^{230}Th	4.8430	0.0137	0.0020	4.8587
^{235}U	7.04×10^8	^{231}Th	4.4693	0.0530	0.1669	4.6891
^{238}U	4.47×10^9	^{234}Th	4.2584	0.0092	0.0014	4.2691

Table 7. Typical isotopic composition in mass and activity of different types of uranium [L35, S15]

Type of uranium	*Mass (%)*			*Activity (%)*			*Activity (Bq) for 1 g*		
	^{238}U	*^{235}U*	*^{234}U*	*^{238}U*	*^{235}U*	*^{234}U*	*^{238}U*	*^{235}U*	*^{234}U*
Natural	99.284	0.711	0.0053	48.2	2.3	49.5	12 400	580	12 474
Depleted	99.807	0.0.199	0.0008	86.1	1.1	12.8	12 400	158	1 843
Enriched (3.5% ^{235}U)	96.481	3.46	0.02831	14.7	3.4	81.8	12 005	2 800	66 703

58. Uranium in rock and soil is in secular equilibrium with the daughters of the decay chain. Uranium-238 decays to ^{234}Th and ^{234m}Pa reaching secular equilibrium within about one year. The ^{238}U decay chain ends with the stable isotope ^{206}Pb. However, disequilibrium between the uranium isotopes can occur through physical and chemical changes involving water. For example, combinations of physical and chemical processes can lead to a separation of ^{238}U and ^{234}U in groundwater [N2]. Uranium-235 and ^{238}U decays contribute to subsequent formation of 10 or more emitters of α, β and γ (figure I). Due to their short half-life, ^{234}Th and ^{234m}Pa (24.1 days and 1.17 min, respectively) are generally present together with ^{238}U.

B. Chemical characteristics

59. Uranium has four valencies, which represent the number of valence bonds that uranium can form with other atoms. The most common valencies of uranium in ores are IV and VI. The conditions of transition from valency IV to VI depend on the redox potential of the medium. Compounds containing hexavalent uranium are much more soluble than those containing tetravalent uranium. Hexavalent uranium forms complexes such as uranyl carbonates (UO_2CO_3) and uranyl sulphates (UO_2SO_4).

60. Uranium can take many other chemical forms. In nature, it is generally found as uranium dioxide (UO_2) with other compounds, such as in pitchblende. Uranium dioxide (UO_2) is the final product in the manufacture of nuclear fuel pellets used in most reactors, and is also present as DU in MOX. Uranium metal is generally alloyed with other elements (Si, Cr, Al, Fe, Mo, Sn, Al).

61. Uranium metal is pyrophoric and extremely reactive. It oxidizes readily to form triuranium octaoxide (U_3O_8) and uranium dioxide (UO_2). Uranium trioxide ($UO_3.xH_2O$) and uranium peroxide ($UO_4.2H_2O$) also exist. Triuranium octaoxide (U_3O_8) is the most stable oxide of uranium and is the form most commonly found in nature. Both triuranium octaoxide (U_3O_8) and uranium dioxide (UO_2) are solids that have low solubility in water and are relatively stable over a wide range of environmental conditions. Through reactions with acids, bases or chelating agents, compounds such as uranyl nitrate, uranyl carbonate, uranyl chloride, uranyl sulphate and uranyl acetate may also be formed. Ammonium diuranate $(NH_4)_2U_2O_7$ is a basic product in the uranium fuel cycle, a component of Yellowcake, which is produced during milling and consists of magnesia or ammonium diuranate (respectively MgU_2O_7 and $(NH_4)_2U_2O_7$). These compounds are converted to uranium hexafluoride (UF_6) prior to enrichment. During conversion, diuranate is converted to uranium trioxide (UO_3), then UF_4, and finally UF_6 is then enriched from ^{235}U ~0.7% to ^{235}U at ~4%. This enriched UF_6 is then converted into UO_2 [D6].

62. As indicated above, different chemical forms of uranium are produced throughout the nuclear fuel cycle [G18]. Uranium-fluorine compounds are encountered in uranium processing, with uranium hexafluoride (UF_6) and uranium tetrafluoride (UF_4) being the two most common. The compound UF_6 is used in the enrichment process of uranium to increase the proportion of ^{235}U, either by gaseous diffusion or by gas centrifuge. It is prepared industrially by the reaction of UF_4 powder with fluorine gas. Uranium tetrafluoride is obtained by treating UO_2 with gaseous fluorhydric acid. It is a non-hygroscopic, non-volatile compound and very soluble in water. In the presence of water vapour, it undergoes pyrohydrolysis and becomes UO_2. When gaseous UF_6 is released into air or as it enters the respiratory tract, it hydrolizes with moisture in air to produce hydrofluoric gas and particulate UO_2F_2. The oxidation states and crystallographic forms of uranium in DU particles have been determined from selected samples collected at different sites in Kosovo and Kuwait contaminated by DU ammunition during conflicts [L39]. Oxidized uranium (+6) was found in large, fragile and bright yellow DU particles released during a fire at DU ammunition storage facilities in Kosovo and Kuwait and crystalline phases such as schoepite

($UO_3 \cdot 2.25H_2O$), dehydrated schoepite ($UO_3 \cdot 0.75H_2O$) and metaschoepite ($UO_3 \cdot 2.0H_2O$) were identified [L39]. These DU particles were rapidly dissolved indicating a high degree of potential mobility and bioavailability. Crystalline phases such as UO_2 and metallic uranium or U–Ti alloy were also determined in impacted DU particles from Kosovo and Kuwait.

IV. HUMAN EXPOSURE

A. Exposure of members of the public

63. Natural uranium exposure of humans occurs through food, water and inhalation. Reviews of autopsy data show that the skeleton is the main site of accumulation of uranium (~80% of total) [B53, K6, S25, U18]. This result, observed in a United States population, was corroborated by measurements made in the United Kingdom [H7, H8] and Japan [I18]. Publications differ about whether the distribution of uranium in the skeleton appears to be uniform [H12] or not [S24]. The age dependence of uranium concentration in the skeleton was also investigated in humans (from six months to 65 years) from vertebrae bones collected in Canada from population exposed to high uranium levels in drinking water [L11]. The data indicated higher uranium accumulation at six months.

64. Fisenne et al. [F6] summarized numerous publications from 12 countries concerning uranium concentration in human tissues, including blood, soft tissue and bone. This analysis demonstrated small differences in uranium concentration in soft tissue and bone. The authors calculated an average of 30 μg for the skeletal burden. The body burden of uranium in humans was estimated between 50 and 60 μg, with 57% in the skeleton, 20% in muscles, 16% in fat, 4% in blood, 2% in the lungs, 1% in the liver and 0.36% in kidneys as presented in figure II [F6]. One publication mentioned uranium levels in the human brain [K6] with values between 0.18 and 0.77 μg of uranium/kg (n=3), corresponding to 0.4 to 0.99%.

65. The Committee in its UNSCEAR 1977 Report [U7] provides further reference concentrations of ^{238}U in various human tissues expressed in mBq/kg: 20 mBq/kg in the lungs, 3 mBq/kg in the liver, 30 mBq/kg in the kidneys, 5 mBq/kg in muscles and 100 mBq/kg in the bones. Despite some differences, these values and those reported by [F6] are similar. High uranium concentrations were also measured in the kidneys in humans [A2, D20, S25]. Calculations made for four age groups (infant, one-year-old, ten-year-old, adult) indicated that long-term chronic uranium ingestion would result in a kidney burden of 6.6% of daily uranium intake for all age groups [C21].

66. Fisenne and Welford [F4] measured an average kidney content of 0.13 μg ^{238}U from 12 New York City dwellers, aged 20–60. An average daily New York City diet of 1.3 μg yields a blood uptake of 0.026 μg. The kidney-to-blood uptake ratio was estimated at 4 and the bone-to-blood uptake ratio at 3.3. Figure III shows the average daily dietary intake of ^{238}U measured in 16 cities in 12 countries [F7].

Figure II. Distribution of ^{238}U in human body [F6]

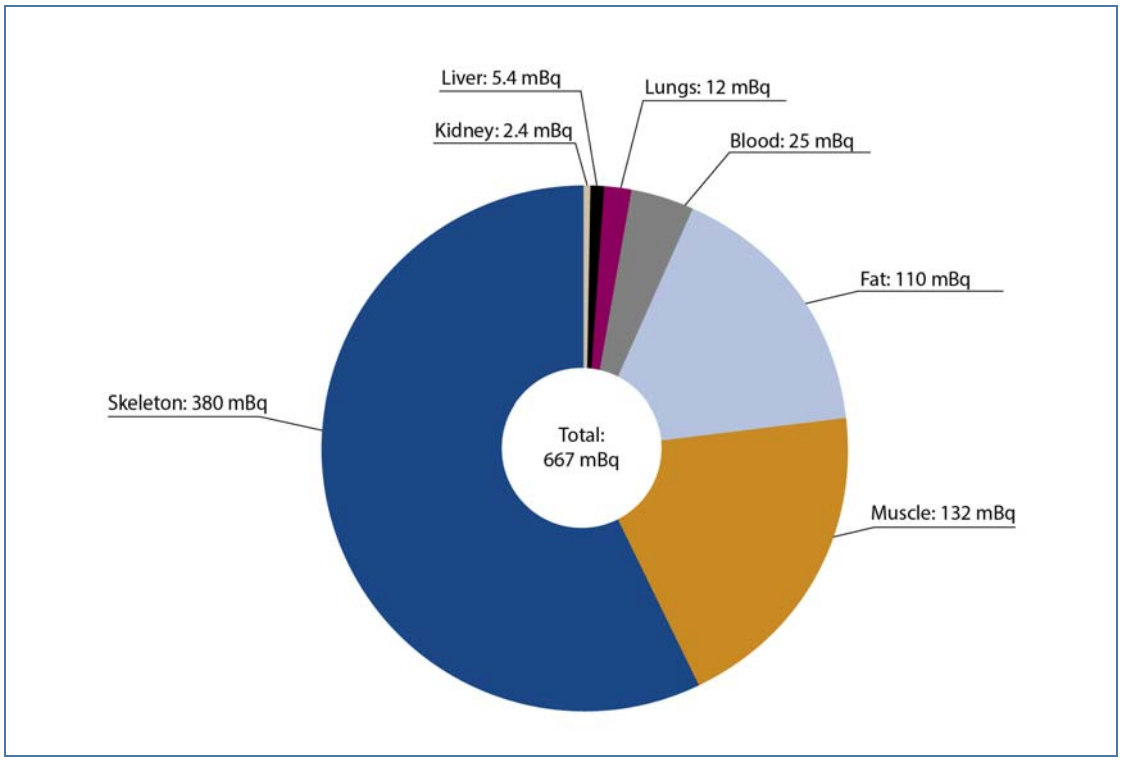
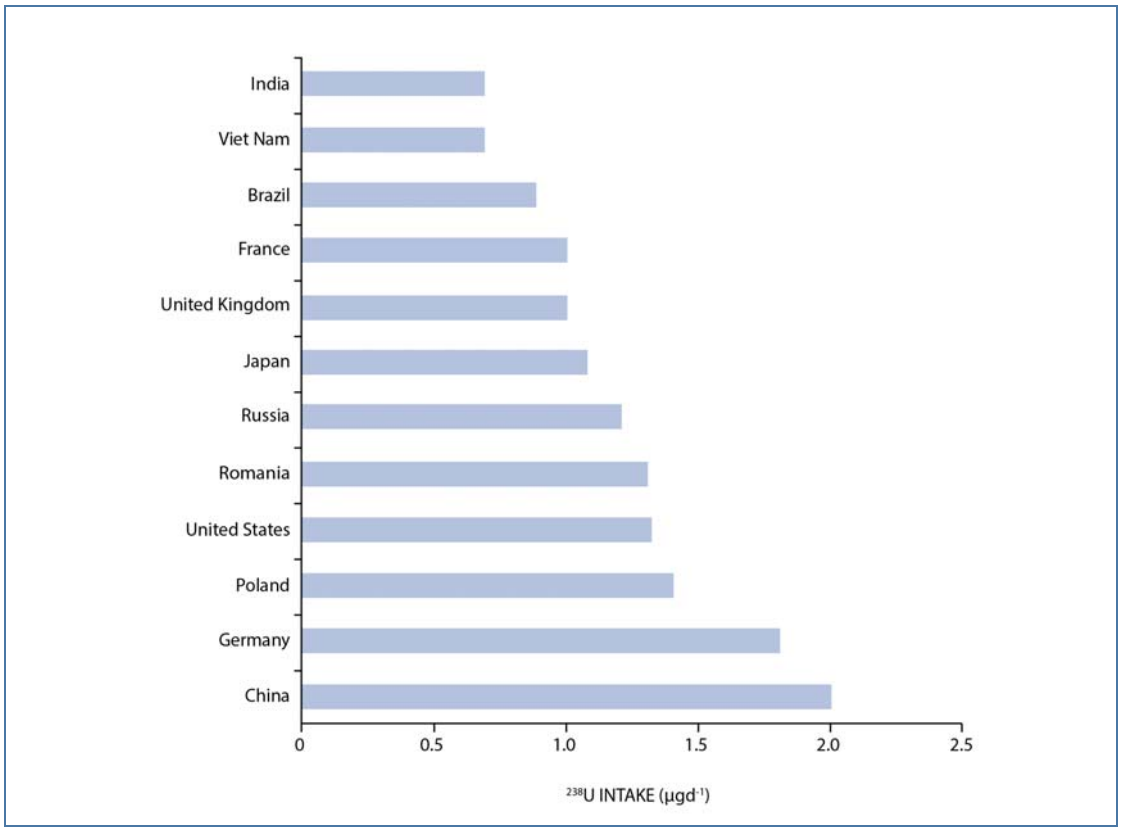


Figure III. Average daily ^{238}U dietary intake measured in 12 countries [F7]



B. Occupational exposure

67. Exposure to uranium may also be relevant to occupational exposure, notably for workers involved in electricity production in nuclear power reactors or at any stage of the nuclear fuel cycle. Each stage of the nuclear fuel cycle is associated with distinct exposure characteristics [D6, D7]. During mining, workers may be exposed to various uranium compounds exhibiting different solubility such as Yellowcake. Further, workers in metal mines, such as underground gold mines, may also be exposed to uranium.

68. Several tissues were collected at the autopsy of workers by the United States Transuranium and Uranium Registries (USTUR) [F3]. Some cases have been analysed following uranium exposure [A34, R31]. Accidental exposure to uranium hexafluoride (UF_6) led to long-term (65 years) retention of uranium in the deep lungs and in thoracic lymph nodes [A34]. High concentration of uranium in tracheobronchial lymph node was also found in other cases without accidental exposure [R31].

69. Often, data on worker exposure are restricted to measurements of external radiation exposure. For instance, Anderson et al. reported that only 16% of the Oak Ridge Gaseous Diffusion Plant (ORGDP) workers were monitored between 1948 and 1988 for internal exposure to uranium by urinalysis [A12]. The difficulty is that monitoring programmes for internal exposure need a combination of bioassay techniques, e.g. urine and faecal analysis, especially in workplaces where compounds of different solubility are handled and also in cases of accidental intakes [J6].

70. Following inhalation of insoluble forms of uranium, the lungs may retain the highest concentrations of uranium [A2, I19]. Adams et al. reported measurements of uranium in kidney and bone following lifetime occupational exposure to uranium aerosols [A2], showing greater retention in bone than kidneys, as seen in data for natural uranium in tissue samples from members of the public.

C. Measurement of uranium

71. The amount of uranium taken into the body can be assessed from external radiation measurements or by bioassay sampling (urine or faeces). The choice and efficacy of each procedure is dictated by the route of intake, the pattern of exposure, the physical and chemical form of the uranium, the time between intake and measurement, and the detection limit of the analytical procedure used [A31, L9, S30].

72. Exposure to uranium can be assessed through the detection of uranium in the urine [B4, C18, C31, D21, L18, L21, M62, S37, S39, W12, W23]. After absorption through oral, dermal and inhalation routes, uranium is excreted in urine mostly as uranyl ions. Uranium urinalysis data have been shown to correlate with airborne uranium exposure when averaged over time and the contribution from ingested uranium is insignificant. Thus, urinalysis can be used to verify the adequacy of air sampling and as a non-invasive method for the estimation of exposure [C18, D9, T7].

73. In vivo external radiation measurements can be used to determine the amount of uranium in the respiratory tract or whole body. The energy of the main gamma emission from ^{235}U is 186 keV. Specialized counting systems (e.g. using germanium semiconductor detectors) are required. The minimum detectable activity (MDA) of uranium in the chest depends on the isotopic mix of ^{235}U and ^{238}U and also on the total amount of uranium in the chest or in the whole body. However, it is of the order of 4 Bq of ^{235}U and 100 Bq of ^{238}U [L25]. When ^{234}Th has reached secular equilibrium with ^{238}U, photon emissions from ^{234}Th may be used in addition to those from ^{235}U to further reduce the detection

limit, by summing the ^{234}Th and ^{235}U photopeaks. Kramer et al. have reported an MDA of 4 mg (i.e. 49 Bq of ^{238}U) [K13]. The detection limit is a function of the chest wall thickness of the measured individual. This parameter must be measured in order to interpret in vivo measurements of uranium in the respiratory tract.

74. Measurement of uranium excreted in urine after exposure is potentially a more sensitive method than chest monitoring to determine the amount of inhaled uranium. The limit of detection by alpha spectrometry is approximately 0.1 mBq of ^{234}U, ^{235}U or ^{238}U in a 24-hour urine sample. Counting times of approximately one week are required to achieve this sensitivity. For natural uranium, a measurement of 0.1 mBq of either ^{234}U or ^{238}U would correspond to about 8 ng of total uranium. Specialized mass spectrometric techniques (such as multicollector inductively coupled plasma mass spectrometry; high-resolution inductively coupled plasma mass spectrometry; or thermal-ionization mass spectrometry) can provide isotopic analysis at levels lower than can be achieved by alpha spectrometry [K12, L20]. Synchrotron-based X-ray techniques (e.g. X-ray fluorescence microscopy, X-ray absorption fine structure, X-ray diffraction may be also used for uranium measurements [C15, P5].

75. The use of faecal assay is confined to intakes by inhalation of relatively insoluble forms of uranium, and dose assessments using these data are subject to substantial uncertainties [D8, J6]. Measurement of uranium in hair could be used as an indicator of body burden in contaminated subjects [B16, I23, J3].

76. Many studies have reported urinary excretion of uranium in humans. The National Report on Human Exposure to Environmental Chemicals [C16] gives uranium concentrations in both µg/L and µg/g creatinine. Expressed in µg/L, mean levels of uranium in the general United States population range from 0.005–0.009 µg/L according to surveys conducted from 1999 to 2012 on 18,266 individuals. Oeh et al. [O1] measured uranium content in 113 urine samples from 63 occupationally unexposed persons in Germany. The urinary excretion of uranium per day was in the range of 1.4 to 77.5 ng with a geometric mean of 13.9 ng and median of 14.4 ng. Höllriegl et al. [H21] measured the uranium content in urine in the general public of Nigeria with creatinine normalized values from <10.4 to 150 ng/L (median 13.8 ng/L) and from 2.52 to 252.7 ng/g creatinine (median 33.4 ng/g). Malátová et al. [M8] measured daily excretion of ^{238}U in urine in the general population (mean 0.311 mBq, range 0.011–2.88 mBq). The measured urinary excretion per day among 40 active uranium miners indicate a mean value of 0.56 mBq with a range of 0.08–2.77 mBq of ^{238}U normalized to 1.7 g daily creatinine excretion [M7]. A study performed in Italy indicated that the daily excretion for the Italian volunteers ranges from 8.2 ng to 59 ng uranium [B1]. The lowest daily excretion was observed for the youngest volunteer (seven years old).

V. BIOKINETICS

77. The main routes of intake of uranium into the human body are ingestion and inhalation. Transfer through intact skin is a minor route. Wounds require consideration in occupational exposure. In general, occupational exposure arises primarily through inhalation of dust containing uranium or following injury. Exposure of the general public arises mainly through ingestion of water or foodstuffs containing uranium. The extent of transfer of ingested or inhaled uranium to blood depends on its chemical form [I10, N2].

A. Inhalation

78. The intake of radionuclides is determined by the air concentration and by the respiratory characteristics of the subjects, particularly the ventilation rate, which changes according to the level of exercise and determines the volume of air inhaled and the deposition of inhaled radionuclides in the airways of the lungs.

79. For radionuclides inhaled in particulate form, regional deposition in the respiratory tract is governed mainly by the size distribution of the aerosol particles [I9]. Deposition fractions of gases and vapours are determined by their chemical form. After deposition in the respiratory tract, absorption and transport of radionuclides involve three general processes. Material deposited in the anterior nasal passage is removed by extrinsic means such as nose blowing. In other regions, clearance is competitive between upward particle transport out of the lungs and dissolution and absorption to blood from the lungs. Particles escalated out of the lungs are subsequently swallowed and pass through the alimentary tract where absorption can occur.

80. The ICRP human respiratory tract model describes the biokinetics and dosimetry of inhaled material and is used to calculate the inhalation dose coefficients that are in general use for radiological protection and scientific purposes [I8]. This model represents the deposition of inhaled radionuclides in the different regions of the respiratory tract, and the clearance of the deposited activity by mechanical transport and absorption to blood. Mechanical particle transport rates are taken to be the same for all material, but are altered by factors such as smoking and disease. Absorption into body fluids depends on the physical and chemical form of the deposited material [I7]. Absorption is modelled as a two-stage process: dissolution (dissociation of material into body fluids) and uptake of soluble material. Uptake into blood is usually treated as instantaneous while dissolution is time dependant and modelled by three parameters: a fraction (f_r) of the activity is rapidly dissolved at a rate (s_r), the remaining fraction ($1 - f_r$) is dissolved at a slower rate (s_s).

81. The absorption rate of a given compound may vary greatly depending on its method of production and history. The ICRP recommends that the absorption rate of any material should be determined from the study of the material itself. In the absence of data, ICRP recommends default parameters for three reference absorption types: Type F (fast), corresponding to rapid and complete absorption of the radionuclide with a half-time of about 10 min; Type M (moderate), corresponding to the absorption of 20% of the activity with a half-time of 10 min; Type S (slow), corresponding to the absorption of 1% with a half-time of 10 min [P4].

82. Hodgson et al. [H20] and Ansoborlo et al. [A15] reviewed the absorption kinetics of uranium compounds handled in the British and French nuclear industry. In vivo experiments in rats and in vitro dissolution studies led to the classification of UO_2 and U_3O_8 as Type S; mixed oxides, UF_4, UO_3 and $(NH_4)_2U_2O_7$ as Type M; and UO_4, $UO_2(NO_3)_2$ and UO_2F_2 as Type F. In addition, these studies provided specific absorption parameter values for each of these compounds. Duport et al. [D32] studied the solubility of radioactive dust present in the workplace atmosphere from three types of Canadian uranium ores—Yellowcake, UO_2 and UO_3—using simulated lung fluid and determined their solubility classification. Solubility studies were conducted in Canada on material from various uranium mining and production facilities [R17]. Bečková and Malátová [B10] studied the solubility of dust samples from the underground uranium mine, Rožná, using simulated lung fluid and calculated specific absorption parameter values for ^{238}U, ^{234}U and ^{230}Th. The dissolution parameters calculated for UF_6 mixture were higher than the current ICRP dose coefficient for Type F uranium (factor 2–7) [A34].

83. Models allow dose calculation from the inhalation of uranium particles in different chemical forms and in several sizes. However, specific data might be needed for remediation and decommissioning

activities potentially generating uranium nanoparticles [T20]. A study of inhaled nanoparticles of uranium in rats [P18] showed that 97% of inhaled particles were deposited in the deep lung and partly translocated to the pulmonary interstitium. Approximately 22% of these deposited particles were rapidly cleared (lung retention half-life of 2.4 h) and for the 78% remaining, the lung retention half-time was estimated at 1,412 days. The ICRP is currently developing material specific absorption parameter values for compounds of uranium and is revising the default parameter values for Type F, M and S compounds.

B. Ingestion

84. Material may reach the alimentary tract either directly by ingestion or indirectly by transfer from the respiratory tract or from the systemic circulation. Absorption takes place largely in the specialized absorptive region of the small intestine [L2]. The extent of absorption of individual radionuclides is dependent on the chemical properties of the element, and also the specific form of the intake. It is quantified by the fraction of element reaching blood following entry in the alimentary tract. The absorption and retention of radionuclides in the human alimentary tract are described in the human alimentary tract model produced by ICRP [I14]. This model depicts transfer of ingested material between alimentary tract regions, faecal elimination and absorption into blood [I14]. In the ICRP model, the fraction f_1 represents the small intestinal absorption, and the symbol f_A refers to the total absorption from the different sectors of the human alimentary tract, including the walls [I14].

85. Soluble uranium is absorbed throughout the small intestine [D25, K9]. Comparative data between species (rabbit, rat, hamster, dog, baboon, pig and human) have been provided by several authors [F11, T19, W26]. Tracy et al. reported a gastrointestinal absorption factor of 0.06% in rats and rabbits [T19] while Frelon et al. reported a value of 0.4% in rats [F11] for uranyl nitrate administrated in drinking water. Leggett and Harrison [L23], Zamora et al. [Z5, Z7] and Wrenn et al. [W27] reviewed the uptake of ingested uranium from the alimentary tract in environmentally exposed human subjects and in volunteer studies. The distribution of f_A values was in a range of 0.001 to 0.063, with daily uranium intake varying from 0.37 to 573 µg. The authors estimated that the best estimate for f_A was 0.009, with no correlation with age, sex, duration of exposure, and total uranium intake. These values are in accordance with those of another study that found fractional absorption (f_A) values in a range from less than 0.1% to about 6% for individual subjects, with the central values from the different studies falling in the range 1–2% and 4% from water for both ^{234}U and ^{238}U [S30]. On the basis of available data, the ICRP Publication 69 [I10] takes the fractional absorption of uranium from diet to be 2% in adults.

86. In newborn infants, fractional absorption may increase by a factor of about two due to the higher intestinal permeability [I14]. This higher absorption in newborns was measured in different species (rats, guinea pigs, pigs, dogs) [S45, S47]. On the basis of animal data, ICRP recommended an f_1 value of 0.04 for infants and 0.02 for anyone more than one year of age [I10]. Chen et al. measured uranium concentrations in 73 bone ash samples of young children residing in a Canadian community known to have an elevated level of uranium in its drinking water supply [C22] and estimated fractional absorption with confidence intervals as wide as 0.093±0.113 for infants and 0.050±0.032 for children of 1–7 years. In another extended study by Chen et al. [C23], the absorption fractions were estimated to be 0.030±0.022 for children and youths of 7–18, and 0.021±0.015 for adults of 18–25 years of age.

87. Experimental studies have shown that fractional absorption depends strongly on the ingested chemical forms. The ICRP is currently revising its Publication 69 [I10] and will adopt an f_A value of 0.002 for relatively insoluble compounds (e.g. UO_2, U_3O_8) and an f_A value of 0.02 for all other more soluble chemical forms [P4]. A biokinetic model was recently developed to describe uptake and retention in hair following ingestion [L34].

C. Absorption

88. Few human data are available on uranium transfer through skin in a report of the National Council on Radiation Protection and Measurements [N3] and in a review of the Armed Forces Radiobiology Research Institute [M17]. Accidents involving workers with extensive skin exposure to uranium have been reported in the other reviews. Lu and Zhao indicated a rapid increase in the uranium level in urine followed by severe kidney dysfunction [L48] with a return to normal values at post-accident day 30. These results were similar to the clinical follow-up made on workers with acute uranium compound intoxication [S16]. Acute renal failure occurred for several days post-accident with recovery one month later. The result of a 33-year follow-up showed that kidney and liver functions were normal [S49].

89. In the use of DU munition, small particles originating from DU dust can contaminate open wounds, and embedded DU fragments may be implanted in muscles. Uranium urine concentrations following accidental intramuscular implantation of metal DU fragments were measured in United States service members exposed to DU through incidents involving DU munition and vehicles protected by DU armour [M25]. Uranium values were from 0.001 to 39.955 µg/g creatinine.

90. Several in vivo studies of rodents with uranium exposure of intact skin [D10, O4, T23] demonstrate that very soluble forms of uranium such as uranyl nitrate and ammonium uranyl tricarbonate are able to diffuse through the skin layer [L47]. The LD_{50} of uranium depended on the species as follows: rabbits >rats >guinea pigs >mice. This toxicity increased with the time and the area of exposure. In vitro Franz diffusion chamber model [T23] and in vivo hairless rat model may be used for evaluation of uranium passage through intact skin [P16, P17]. An in vivo study showed that a significant uptake of uranium from a uranyl nitrate solution could occur within the first six hours of exposure after skin contact. Furthermore, as high uranium concentration remained present at the deposit site for up to 24 hours after contamination, skin provided a reservoir for uranium that remained bioavailable [P17].

91. Percutaneous diffusion of uranium was also studied on damaged skin from hairless rats, following an abrasion (*stratum corneum* removal) [P15, P17]. In vitro study of biopsies showed that the percutaneous absorption of uranium increased with the impairment of the *stratum corneum.* Ex vivo studies with biopsies showed an increase in the diffusion of uranium through skin after abrasion compared with that through intact skin. These results have been confirmed in vivo in hairless rats [P16].

92. The NCRP's biokinetic model describes the mobilization of radionuclides, including uranium, entering the body through a wound to blood [N3]. Three wound retention categories were described, corresponding to contamination with soluble forms, colloids, particles or fragments. The uranyl ion (UO_2^{2+}) was classified as a weakly-retained radionuclide, and UO_2 oxide particles behaved rather as strongly-retained radionuclides.

D. Systemic distribution, retention and excretion

93. The translocation of uranium to blood strongly depends on the physical and chemical form of the initial compound [A15]. After its absorption to blood, uranium is present mainly as uranyl ions complexed to proteins (e.g. transferrin, albumin) or bicarbonate anions [A16]. The main sites of deposition of uranium from the circulation are the skeleton, kidneys and general soft tissues. Human and animal data show that urinary excretion is rapid with about two thirds of uranium reaching blood excreted in the first 24 hours and a further 10% over the next 5 days. Most of the remaining uranium is excreted over a period of a few months, but a small percentage of the amount injected may be retained for a period of years [L22].

94. The work of Leggett [L22] was used by ICRP [I11] to propose a reference model for uranium biokinetics. This model is constructed within a physiologically-based framework that is also applied to the alkaline earth elements. Rates of uranium transfer between plasma, red blood cells, skeleton, liver, kidneys, other soft tissue and excretion pathways are based on measurement of uranium in humans and animals and consideration of the physiological processes. The model considers age-related changes in organ and tissue uptake and retention of uranium. The ICRP will use the same model in ongoing revisions of dose coefficients [P4].

95. The United Kingdom Royal Society [R28] used the ICRP's biokinetic models to estimate the concentrations of uranium in the kidneys following chronic exposure over one year at a constant daily uptake of 1 µg of uranium to blood. The estimated uranium concentration in the kidneys was 0.0056 µg/g kidney after one year and 0.011 µg/g kidney after 50 years of contamination. This result is not in accordance with the result of other studies. For instance, a study measured ^{238}U in diet and kidney tissue in residents of New York and showed that a daily intake of 1.27±0.03 µg resulted in a uranium concentration in the kidneys of 0.00043±0.26 µg/g that was constant over ages <20 years to >60 years old [F4].

96. Several studies have found that uranium can be incorporated into brain tissues [B11, G10, L30, O7]. It has been demonstrated by an in situ rat brain perfusion method that uranium is able to cross the blood-brain barrier [L27] but the mechanism by which uranium is transferred to the brain is unknown. After acute, subchronic or chronic exposure, low uranium concentrations are found in the various structures of the brain [B6, F8, H24, L38, P11, P12]. The level of uranium in the brain, notably in olfactory bulbs, was greatest after inhalation [H26, T15]. Such uranium concentration in olfactory bulbs as compared to other cerebral structures is attributable to the direct transfer of uranium via olfactory receptor neurons [I6, T15].

97. Mean values of uranium concentrations in human breast milk were reported as 0.03 µg/L (0.76 mBq/L) [W9] and 0.30 µg/L (7.6 mBq/L) [C1]. The daily intake of uranium of mothers is 0.03±0.019 µg/kg (mean±SD) [W9]. These values are in accordance with values measured in several animal studies, which suggest similar transfer processes (see also table 3).

E. Materno-fetal transfer

98. Few data are available on materno-fetal transfer in humans and in animals. Some publications have reported uranium concentrations in fetal samples [B46, B47, L26, S17, W10], in placenta [B47, S17, W10], in amniotic fluid [C14, S17] and in cord blood [G22].

99. Ham et al. [H7] reported uranium concentrations measured in human fetus and Bradley and Prosser in placenta samples [B47]. The activities of ^{238}U ranged from 0.1 to 9 mBq/kg in the fetal samples of human fetus and from <1 to 11 mBq/kg in placenta samples. Uranium concentrations ranged from 0 to 0.2 µg/L (mean=0.024 and median=0.005) in human amniotic fluid [C14] and from 0.003 to 0.834 µg/L (mean=0.104 and median=0.057) in cord blood [G22].

100. An experimental study performed by Legrand et al. on pregnant rats exposed to uranium via drinking water (40 and 120 mg/L) indicated no elevated uranium concentration in exposed fetuses as compared to control animals [L26]. Another study performed by Sikov and Mahlum on pregnant rats after injection indicated that only a small fraction of the injected nuclide (148 kBq of ^{233}U) entered the fetus and the distribution within the fetus was dissimilar from that observed in the dam [S17]. Only 0.06% of injected dose/g body weight was measured in fetal kidneys at 20 days as compared to 5.18 in

the dam. The authors also reported 0.03% injected dose/g body weight in fetus, 0.05% in placenta and 0.001% in the amniotic fluid [S17].

101. The ICRP [I12] has provided biokinetic and dosimetric models and dose coefficients for the embryo, fetus and newborn as a result of intake of radionuclides by the mother. The term fetus refers to the developing human offspring after the eighth week of pregnancy. The equivalent dose to the embryo is assumed to be the same as that to the uterus wall and proportional to the concentration of uranium in maternal soft tissue. The ICRP uses a simple approach for the calculation of fetal doses for the majority of elements and their radioisotopes, including uranium, considering data collected from studies of animals and humans [I12, I13]. Thus, fetal doses from uranium are calculated on the basis of relative concentrations of uranium averaged over the whole body of the fetus (C_F) and that of the mother (C_M). A conservative C_F:C_M ratio of 1 is used for intakes of uranium during pregnancy. The distribution of uranium in the fetus is assumed to be 80% to skeleton, 2% to kidneys, and 18% to other tissues [I12].

VI. DOSIMETRY

102. Absorbed doses in tissues are calculated using dosimetric models such as those of ICRP (e.g. [I7, I10, I11]) and of the Medical Internal Radiation Dose (MIRD) committee [B39]. The absorbed dose is the fundamental quantity that is estimated and averaged over particular tissues and organs. The distribution of absorbed dose from internally deposited radionuclides, here the uranium isotopes, depends on a number of factors, including the distribution of the radionuclides within organs and tissues, and the penetration and range of radiation emitted from the radionuclides. Dosimetric models have been developed for this purpose.

103. Absorbed doses from photons and electrons are calculated by applying Monte-Carlo codes of radiation transport to anthropomorphic computational phantoms representing a reference person [I15]. Alpha particles are considered to be absorbed in the region where they are emitted, except for the skeleton, lung, urinary bladder and alimentary tract where the respective positions of the alpha-emitting radionuclides and of the sensitive target cells are taken into account to assess the dose absorbed by the target cells. In most organs and tissues, local activity and also the radiosensitive target cells are assumed to be uniformly distributed. However, in these few specific tissues, the identification of the putative radiosensitive cells allows a more precise definition of the source and target geometry of irradiation, which is of concern for the short-range alpha particles emitted by uranium isotopes. The target cells identified in the thoracic airways include basal and secretory cells in the bronchial epithelium, endothelial cells such as those of capillary walls, and type II epithelial cells in the alveolar-interstitial region [I8].

104. Following the ICRP, the equivalent dose in a region T, H_T, is defined as:

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

where $D_{T,R}$ is the average absorbed dose in region T, due to radiation of type R; w_R is the radiation weighting factor for radiation R and is equal to 1 for photons and beta particles and 20 for alpha particles [I10, I15].

The effective dose E is defined as a weighted average of equivalent doses to radiosensitive tissues of the body:

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

where w_T is the tissue weighting factor for tissue T, with the sum of w_T being 1. The committed effective dose $E_T(\tau)$ is defined as the effective dose delivered over the time τ following intake of a radionuclide. The τ is usually set to 50 years for adults and for children up to the age of 70 years so as to cover life-long irradiation [I10].

105. Doses from the inhalation or ingestion of unit mass of uranium can be determined by multiplying the corresponding dose coefficient (i.e. for ^{238}U, ^{235}U and ^{234}U) by the isotopic activity for each level of enrichment [I7, I11].

106. The ICRP provides reference dose coefficients per intake of uranium isotopes for workers [I7] and members of the public [I10] in accordance with the international safety standards of the IAEA [I4]. The values for inhalation by workers and ingestion by members of the public are given in tables 8 and 9, respectively. The f_1 values of the ICRP model depend on age, and the model for the systemic behaviour of uranium is also age-dependent, and so the committed effective dose per unit intake calculated for ingestion of soluble uranium by members of public exhibits age-dependence (table 9).

Table 8. Committed effective dose per intake (Sv/Bq) for inhalation by workers (for 5 μm AMAD particulates) [I7]

Solubility group of uranium compound: F (fast soluble), M (moderately soluble) and S (slowly soluble)

Isotope	*Absorption type*		
	F	*M*	*S*
^{234}U	6.4×10^{-7}	2.1×10^{-6}	6.8×10^{-6}
^{235}U	6.0×10^{-7}	1.8×10^{-6}	6.1×10^{-6}
^{238}U	5.8×10^{-7}	1.6×10^{-6}	5.7×10^{-6}

Table 9. Committed effective dose per unit intake (Sv/Bq) for ingestion of soluble uranium by members of public [I10]

Isotope	*Age at intake*					
	3 months	*1 year*	*5 years*	*10 years*	*15 years*	*Adult*
^{234}U	3.7×10^{-7}	1.3×10^{-7}	8.8×10^{-8}	7.4×10^{-8}	7.5×10^{-8}	5.0×10^{-8}
^{235}U	3.5×10^{-7}	1.3×10^{-7}	8.5×10^{-8}	7.1×10^{-8}	7.0×10^{-8}	4.7×10^{-8}
^{238}U	3.3×10^{-7}	1.2×10^{-7}	8.0×10^{-8}	6.8×10^{-8}	6.7×10^{-8}	4.5×10^{-8}

VII. BIOLOGICAL EFFECTS

A. Chemical versus radiological toxicity

107. Uranium represents a particularly difficult problem for internal emitter studies because of its chemical and radiological toxicities. It is a radioactive heavy metal, and it is difficult to characterize differences in responses to the metal component alone, the radioactivity alone, or the possible combined effects of both. Some studies on DU have attempted to define the metal component, however these are limited by the presence of radioactivity.

108. Despite the dual toxicity of uranium, few studies investigate the respective parts of its chemical and radiological toxicities. As with all chemicals, the chemical toxicity of uranium is linked to its ability to interfere with compounds and biochemical processes in living organisms. The chemical action of all isotopes and isotopic mixtures of uranium is independent from the specific activity because chemical action depends only on chemical properties [W13]. However, it is dependent on its physical and chemical forms. For instance, the NOAEL values measured for uranium effects vary depending on the absorption type of uranium compound, i.e. F (fast soluble), M (moderately soluble) and S (slowly soluble). Different reports gave NOAEL values as a function of the administration mode and the exposure duration [A31, W14].

109. Concerning the radiological hazard of uranium, alpha particles do not penetrate beyond the outer layer of skin, except in regions of thinner skin (the depth varies typically in the range 20–100 μm). The impact on health of alpha particles of uranium is expected mainly after internal contamination and depends partly on the route of exposure (inhalation or ingestion) [W14].

110. Both natural uranium and DU pose primarily chemical rather than radiological hazards in the short term. The toxicity of uranium depends on its chemical form and the route of exposure [A31]. The potential health effects arising from uranium exposure are discussed below. Some effects are related to the chemical toxicity of uranium, notably renal effects, while other effects are mainly due to the radiological toxicity of uranium, such as tumorigenic effects.

111. The relative importance of chemical and radiological toxicities of uranium thus depends on the degree of enrichment of ^{235}U (and ^{234}U), the compound solubility, the chemical speciation and the mode of incorporation [A31, S46, T9]. Chemical toxicity from uranium exposure appears mainly in the kidneys and is assumed not to occur below a threshold concentration. The thresholds given in the literature are most often derived from a NOAEL in animal experiments with the application of an appropriate safety factor for transposition to humans [A31]. Human autopsy data are used to confirm these observations [A31, S43].

112. Stradling et al. discussed anomalies between radiological and chemical limits for uranium after inhalation by workers [S41]. As a consequence of the different procedures used in their calculation, they are incompatible and adherence to one limit may result in a breach of the other. They concluded that for chronic intake by members of the public, it can be deduced that a unified exposure level of 0.5 μg/kg per day or a daily intake of 35 μg would be acceptable in most cases. More recently, Thorne and Wilson proposed higher limits corresponding to 2 μg/kg per day or a daily intake of 140 μg [T9].

B. Kidneys

113. The limited human studies suggest that damage to the kidneys can be detected following chronic exposure that results in uranium concentrations as low as 0.1 μg per gram kidney [R28]. Human studies also suggest that acute intake which leads to a peak uranium level of about 1 μg per gram kidney can lead to detectable kidney dysfunction [R28]. Some authors have aimed to predict renal concentrations in human populations exposed to uranium for dose assessments [C21, S31]. In the epidemiological section some human data are presented of populations exposed to high uranium concentrations in drinking water.

1. Acute exposure

114. Morphological renal modifications induced by uranium (from 0.1 mg/kg after injection) were reported in rodents in several experimental studies, suggesting that the kidneys are the major target organ of acute uranium toxicity independent from the route and duration of exposure [B25, D17, G27]. Histopathological changes, including degenerative changes or necrosis of the proximal tubular epithelium and glomeruli, were reported after acute exposure in rats [D12, M16]. Further, some histological alterations were noted in renal tubules of rats following chronic exposure with elevated concentration of uranium [G10, O7]. Thus, acute exposure may lead to alteration of glomerules and tubules, whereas chronic exposure to uranium seems to affect only tubular functions. Following intramuscular injection of DU, rats undergo dose-related tubular necrosis and glomerulonephritis. After 30 days, glomerular damage is reversible in rats at all doses (0.1–1 mg/kg) but there is a dose dependent delay in the initiation of the regeneration, seen first in the low-dose group (0.1 mg/kg) [Z17].

115. An experimental study performed by Shiquan et al. on rats considered a wide range in uranium concentrations of 5, 2.5, 1.0, 0.5, 0.25, 0.1, 0.05, 0.025, 0.01, 0.0075, 0.005, 0.0025 and 0.001 mg/kg, administered by intraperitoneal injection as uranyl nitrate [S14]. Doses from 0.01 to 0.05 mg/kg induced slight renal damage. The lowest dose that induced renal damage in all rats of one group was 0.1 mg/kg. At the highest dose (5 mg/kg), necrosis of the proximal tubular epithelium was observed after 6–12 hours, and half the rats died after 6–8 days. Primary damage to the kidneys was necrosis of the proximal tubular epithelium. After repair with regeneration, different degrees of fibrous scarring were found in the kidneys.

116. The third segment of the proximal convoluted tubule is the most affected site in the kidneys of rats [G11] and humans [M9]. Experimental studies performed on dogs [M63] demonstrated that the complexed uranium (VI) is filtered from blood via the glomeruli. In the proximal tubule, water is reabsorbed and uranium is concentrated. As urinary flow acidifies, uranium (VI) complexes are dissociated and uranium can bind epithelial membrane proteins. Uranium kidney retention thus increases with urinary acidity and decreases with uranium complexation.

117. Table 10 summarizes studies of the toxic effects of uranium on the kidneys of rats following acute exposure. Biological effects indicating toxicity of uranium to the kidney were noticed starting from 0.1 mg/kg [Z17] to 126 mg/kg of body weight [F18]. Most of the studies were done on rats and showed a decreased creatinine clearance and an increased electrolyte or protein excretion, indicating tubular alterations of the kidneys [B5, F18] that can also be associated with liver alteration as shown by increased transaminase level [G29].

118. Shude and Suquin et al. reported dose evaluation and medical follow-up of a case of acute uranium compound intoxication [S16, S49]. A nuclear worker received both thermal and acid burns. A

solution of uranyl nitrate hexahydrate was spurted on his body, and uranium was absorbed through the skin to blood. Acute renal failure and toxic hepatitis occurred during several days post-accident and recovery occurred one month later. The amount of uranium taken into the body as a result of this incident was calculated to be 116 mg [S16, S49]. The result of 33 years' follow-up showed that the function of kidney and liver were normal. Chromosome aberrations of peripheral lymphocytes were observed, including ring, fragment and dicentric. The results of other examinations were at normal levels, including peripheral blood, bone marrow, immune system, cardiovascular and respiratory function, endocrine and metabolism [S49].

Table 10. Summary of studies of toxicity of acute exposure in kidneys of adult rats

ip: intraperitoneal; im: intramuscular; iv: intravenous; BUN: blood urea nitrogen; GFR: glomerular filtration rate; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alkaline phosphatise; BW: body weight

Uranium compound	*Exposure conditions*	*Post-exposure follow-up*	*Sex*	*Biological effects*	*Study references*
Uranyl nitrate	ip 0.001–5 mg/kg	8 days	Male	Necrosis of the proximal tubular epithelium Damage repair with renal fibrous scar Half died after 6–8 days in the highest-dose group	[S14]
Uranyl acetate	ip 0.1–1 mg/kg	30 days	Male	Increased creatinine, BUN and albumin at high dose in serum	[Z17]
Uranyl nitrate	ip 0.5 mg/kg	5 days	Male	Increased creatinine, urea, cholesterol, phospholipids in plasma	[B5]
Uranyl fluoride	ip 0.66 mg/kg	110 days	Male	Decreased kidney weights Increased LDH, AST in plasma and protein, albumin in urine	[D12]
Uranyl nitrate	im 0.2–2 mg/kg	28 days	Male	Decreased plasma ALT, AST, protein and increased urea, creatinine, ALP	[F18]
Uranyl nitrate	ip 10 mg/kg	28 days	Male	Increased concentrations of sodium and protein in urine Decreased GFR	[H6]
Uranyl nitrate	ip 11.5 mg/kg	3 days	Male	Increased creatinine, urea, ALT, AST plasma levels	[G25]
Uranyl nitrate	im 7.9–126 mg/kg	28 days	Male	Decreased BW and died after 3–7 days	[F18]
Uranyl nitrate	ip 5/10/20 mg/kg	2 days	Male	Histopathological lesions Increased plasma creatinine and urea plasma levels	[A18]
Uranyl nitrate	ip 50–500 µg/kg	21 days	Female	Renal morphological alterations (at the first dose, becoming increasingly prominent with higher doses)	[B17]
Uranyl nitrate	iv 15/25 mg/kg	17 hours	Female	Changes in endothelial cell morphology for the higher dose	[A33]

119. Other high human exposure—accidental or deliberate—were reported. Roszell et al. reported 27 cases of human exposure to uranium and the resulting kidney effects [R24]. The uranium burden estimated in the kidneys ranged between 10 μg/g kidney after accidental inhalation of UF_4 powder [L48] and 100 μg/g kidney after deliberate ingestion of 15 g uranium acetate [P9]. Early symptoms of renal failure were noted in the first weeks after exposure, with renal dysfunction observed in some cases until 6 [P9] or 18 months [L48] after exposure. Kathren and Moore re-evaluated the intake and deposition of soluble natural uranium compounds in three men accidentally exposed in an explosion in 1944. One of the three exposed individuals showed an altered clearance pattern for uranium shortly after the accident, possibly from pulmonary oedema associated with concomitant exposure to acid fumes. However, medical examinations of two of the men 38 years after the accident revealed no detectable deposition of uranium [K4].

120. Table 11 provides a summary of the effects of chronic uranium exposure on the kidneys of experimental animals. Conversely, chronic exposure did not clearly induce a toxic effect on the kidneys of mammals, with duration of exposure from three to twelve months and exposure level from 0.02 to 200 mg/kg. Tissue alteration of the tubules or glomerules was observed only for uranium doses above 400 mg/kg [G10, Z13]. After a nine-month chronic exposure to uranium via ingestion of uranium-contaminated drinking water, the kidneys of rats did not show signs of histological lesions for uranium renal levels >3 μg/g (3 μg/g for 120 mg/L [D29] and 6 μg/L for 600 mg/L [P23]).

121. Gilman et al. [G10] noted that effects on the kidneys could be seen at uranium levels of 0.06 mg of uranium per kilogram of body weight per day for male rats. Nevertheless, no rise in histopathological severity with increasing dose was reported: histological lesions starting from the lowest concentration (0.96 mg/L, 0.09 mg/kg body weight) were not significantly different from the kidney lesions observed for the highest concentration (600 mg/L) [G10, G11]. No clear dose-dependent effect was observed after chronic exposure. Indicators of kidney function after acute exposure (0.1–10 mg/kg) included the concentrations of blood urea nitrogen (BUN), creatinine in blood or protein in urine [B5, F18, G23, H6, O7]. Conversely, only limited changes were identified for chronic exposure to uranium in drinking water (2–16 mg/kg) [G11, O7] or from implanted DU pellets (200 mg/kg) [P12, Z13, Z14].

122. Various urinary parameters—including levels of urea, glucose, creatinine, total protein, and albumin and also activities of LDH and N-acetyl-beta-D-glucosaminidase (NAG), and glucose excretion—had the most persistent effect after chronic exposure [G10]. Complementary studies showed that chronic low dose uranium exposure did not modify the nephrotoxic effects of gentamicin renal response as evidenced by the renal tissue levels of kidney injury molecule (KIM-1), osteopontin, and kallikrein [R27]. The results observed with osteopontin were different from those found in clinical studies, which indicated a decreased osteopontin level in urine [P30]. Gentamicin-induced increase in renal levels of KIM-1 was augmented in rats previously exposed to uranium as compared to uncontaminated animals.

123. In a dose-response study (0.27–40 mg/kg) of chronic oral exposure of rats, nephrotoxic and pro/anti-oxidant effects were analysed after three- and nine-month exposure [P23]. The uranium content of the kidneys was proportional to uranium intake after three and 9 months of contamination. It reached 6 μg/g of kidneys for the highest uranium exposed group, a nephrotoxic level for acute intake. Uranium microdistribution analyses showed that it was found mainly in the nucleus of renal proximal tubular cells and to a lesser extent in other renal structures. Nevertheless, no renal impairment was observed according to histological analysis or measurements of sensitive kidney biomarkers such as KIM-1, β2-microglobuline or retinol binding protein. Uranium contamination appeared to reinforce the antioxidant system in the kidneys as the glutathione pool increased dose-dependently up to tenfold.

Table 11. Summary of studies of biological effect of chronic exposure to uranyl nitrate on kidneys of male adult animals

PCT: proximal convoluted tubule

Species	*Exposure conditions*	*Follow-up*	*Biological effects*	*Study references*
Rat	Oral 100 mg/kg	27 days	Histopathological lesions (increased when exposure duration increased)	[G15]
Rat	Oral 0.02–40 mg/kg	91 days	Decreased haemoglobin, erythrocytes, glucose not correlated to the concentration in drinking water Histopathological lesions in the lowest group	[G11]
Rat	Oral 2.7 mg/kg	275 days	Decreased plasma vitamin D and vitamin D target genes in the kidney tissue	[T11]
Rat	Oral 2.7 mg/kg	275 days	Following single exposure to acetaminophen (paracetamol), increased PCT necrosis of the kidney	[G26]
Rat	Oral 2–16 mg/kg	28 days	Increased glycaemia whatever the dose in plasma	[O7]
Mouse	Oral 13–26 mg/kg	122 days	Decreased urea and increased creatinine in plasma	[T4]
Rabbit	Oral 0.02–400 mg/kg	91 days	No biochemical changes Kidney histopathological lesions in the highest group	[G10]
Rat	Muscle implantation 200–600 mg/kg	91 and 360 days	Increased plasma urea, creatinine and urinary beta-2 microglobulin and albumin	[Z14]
Rat	Oral 0.014-8 mg/kg	275 days	No biochemical changes No renal histopathological lesions	[D29]
Rat	Oral 0.27–40 mg/kg	91 and 275 days	Glutathion increase dose-dependently and lipid peroxidation decrease in kidney No nephrotoxity (biomarkers and histology)	[P23]

124. A study by Silver et al. provided information regarding non-malignant chronic kidney disease [S19], which proved to be non-significant. There was a trend in chronic renal failure deaths in the Colorado uranium miller cohort with duration of uranium milling employment (SMRs of 1.27, 1.33 and 1.53 for 1–2, 3–9 and ≥10 years of employment, respectively) [P21]. However, when treated end-stage renal disease for those receiving renal dialysis or kidney transplants, the incidence was evaluated using the ESRD program (End Stage Renal Disease) date, there was no excess (SIR=0.71, 95% CI: 0.26-1.65). In the Fernald cohort, mortality from chronic renal disease was not related to uranium exposure [S19] (see also table 18). Other studies of uranium worker cohorts indicated no significant overall excesses of chronic kidney disease death [B38, C20, D33, M26, M27, P24]. Some renal effects were studied in humans following chronic exposure to uranium via drinking water. These data are shown in appendix A, table A11, which summarizes the published literature on the health effects of human exposure to uranium through ingestion of surface or groundwater.

2. Influence of age

125. Few studies have investigated the influence of age at exposure on renal toxicity. The first results considering this issue were published before 1920 for studies using dogs [M3]. The author demonstrated that older animals developed more severe uranium poisoning than young animals, associated with more marked histological alterations, leading to an impaired functional capacity [M3]. This result was corroborated by a more recent experiment, also performed on dogs [P10]. Uranium effects on renal function (glomerular filtration rate) were more severe in older (3/4 weeks) than in younger dogs (1/2 weeks). Recent publication of an experiment performed on rats with 0.1–2 mg/kg of uranium acetate indicated a higher uranium concentration in the kidneys of neonatal animals than in prepubertal or adult animals [H22].

126. Magdo et al. studied the effects of the high uranium concentration in drinking water of a private wells used by a family (two adults and five children). The authors measured concentrations of up to (1,160 µg/L) in the groundwater [M5]. The authors evidenced a nephrotoxicity in the youngest family member (a three-year-old child), demonstrating the highest sensitivity to uranium exposure. This case shows potential for significant residential exposure to naturally occurring uranium in well water. It highlights the special sensitivity of young children to residential environmental exposures, a reflection of the large amount of time they spend in their homes, the developmental immaturity of their kidneys and other organ systems, and the large volume of water they consume relative to body mass [M5]. However, this result appears inconsistent with observations made in young rodents.

3. Biological mechanisms

127. According to Leggett [L21], uranium binds to the luminal brush-border membrane of tubules. This binding decreases reabsorption of sodium and other compounds, resulting in an increased urinary excretion of proteins, glucose, catalase, phosphate, citrate and sodium without causing cellular damage [B25]. Uranium can then separate from the luminal membranes by a number of mechanisms including association with complexing ligands from the urinary tubular flow, detachment of uranium-bound microvillosities, and elimination of dead cells. The mechanism by which uranium then enters tubular cells has been investigated. Once in the cytoplasm, uranium accumulates in lysosomes, where it precipitates with phosphate, forming microcrystals at high concentrations [M47]. This process induced destruction of the lysosome.

128. The mechanisms of uranium effects on the kidneys have not been fully elucidated. The relations between uranium penetration into and distribution within cells and its toxicity was analysed in kidney proximal tubular cells. Some authors posited that uranium did not need to penetrate cells to exert its toxic effect [L21, M68] while others posited that it did [L1, M47]. Rouas et al. have suggested that the physical form of uranium (soluble or precipitate) and its intracellular localization play a role in cell toxicity [R26]. They suggested that uranium may be visualized in the nuclei in kidney cultured cells exposed to uranyl nitrate. Experimental studies have indicated that uranium exposure of animals (rats or mice) at 5–25 mg/kg may induce changes in solute transport [G11, T5], protein biosynthesis-related genes [T4, T5] or cell signalling [P26, T5].

129. Several studies reported effects of uranium on renal transporters, Na^+,K^+-ATPase [B48], sugar transporters [G17, N4, R19], sodium-dependent phosphate cotransporters [M68, M69] and organic cation transporters [M4, S13] but these effects were studied only in vitro using relatively high uranium concentrations.

130. Mitochondrial dysfunctions have recently been demonstrated in rats after injection at 0.5, 1 and 2 mg/kg per intraperitoneal injection [S9]. Isolated mitochondria from the uranyl acetate-treated rat kidney showed a marked elevation in oxidative stress accompanied by mitochondrial membrane potential collapse as compared to the control group. In addition, direct incubation of isolated kidney mitochondria with uranyl acetate (50, 100 and 200 μM) suggested that uranyl acetate can disrupt the electron transfer chain at complex II and III.

131. To investigate the influence of uranium speciation on its toxicity, cells representative of rat kidney proximal epithelium (NRK-52E) have been exposed to uranyl-carbonate and -citrate complexes, because they are the major complexes transiting through renal tubules after acute in vivo contamination. When citrate is added to the exposure medium, the predominant species is uranium (VI)-bicarbonate. Nonetheless, citrate increases uranium (VI) toxicity and accelerates its intracellular accumulation kinetics without inducing precipitation [C10].

132. Uranium can induce cell death but the exact mechanisms are still unclear. Some proposed mechanisms include apoptosis or genotoxicity [M54, T6, V5]. The mechanisms of acute toxicity of uranium (from 50 to 500 μM) have been studied in renal cell lines and have shown a specific uranium signature characterized by the downregulation of tubulin and actin [P27]. The most investigated mechanism to explain uranium toxicity is the oxidative stress response, investigated both in vitro on cell cultures and in vivo following acute or chronic exposure in rats and mice [B5, S9, T4, T5, T6]. The results of these studies suggested uranium-induced oxidative stress imbalance with an increased reactive oxygen species production associated with a depletion of endogenous cellular antioxidants for elevated concentrations administrated to cells (>400 μM) or to animals (>0.5 mg/kg).

133. Several studies have focused on the interaction between iron metabolism and uranium, in conjunction with the affinity of these two elements for some proteins such as transferrin, ceruloplasmin and ferritin [V8]. These studies revealed changes in gene expression and protein carriers of iron, DMT1 (Divalent Metal Transporter Type 1) and Fpn (ferroportin), in the liver and kidneys [B19]. A similar study [D19] performed on rats chronically exposed to uranium in drinking water (2.7 mg/kg/day) showed the appearance of iron granules (aggregates) in the kidneys, indicating that chronic contamination by uranium could cause long-term changes in the regulation of iron metabolism. A recent study using surface plasmon resonance techniques has shown a strong affinity of fetuin-A protein for uranyl ions even though this protein is present in a very small amount [B7].

4. Conclusion

134. The kidneys are known as the most sensitive target organ after acute exposure, on the basis of well-documented studies. Studies on rodents (mice and rats) indicated that injury to the kidneys occurs from 0.1 mg/kg whole body and renal concentrations of >3 μg/g, targeting the third segment of the proximal convulated tubule. Conversely, data on chronic exposure to low uranium doses are more recent and have not shown clear nephrotoxic effect at 2–20 mg/kg and no specific biomarkers have been identified to date. New blood plasma or urinary biomarkers of the renal function or integrity have been investigated in experimental or clinical studies, with a view to allowing a precise diagnosis of the kidney function [G27]. Mitochondrial dysfunction seems to be involved in toxic mechanisms of uranium, but the mechanisms of its toxicity are not fully elucidated to date, especially after chronic exposure to low and high doses. Further experimental studies are necessary for a better comprehension of the renal alteration process and the identification of more specific biomarkers of kidney alteration.

135. Chemical effects on the kidneys are usually assumed not to occur below certain threshold concentrations of uranium; most often, these findings have been derived from animal experiments with the appropriate safety factors applied to human exposure [A31]. Maximum concentrations over 3 μg of uranium per gram of kidney have been used as the basis for occupational exposure limits (e.g. [H20, L21]). Leggett [L21] suggested that the occupational limit based on 3 μg of uranium per gram of kidney is about tenfold too high for non-occupational exposure. Indeed, some human studies suggest that damage to the kidneys can be detected following chronic exposure that results in uranium concentrations as low as 0.1 μg per gram kidney [R28]. Thorne and Wilson [T9] suggested 30 μg U/kg kidney as a level below which effects will not be observed. Further, following a review of the existing literature, Leggett et al. have recommended that "the concentration of uranium in the kidney should not exceed 1 μg U/g kidney at any time" [L25].

C. Bone

1. Acute exposure

136. Several animal experiments demonstrated a high uranium accumulation in bones of rats and dogs [A23, A24, P31]. Several studies performed on rats have investigated the effects of uranium on bone physiology. These studies found an impairment of bone growth and bone formation [P33, U1, U2]. These effects were associated with inhibition of endochondral ossification in mice [B45] and in rats [D15]. Other rat experiments indicated that uranium induced ultra-structural alterations in osteoblasts [T3]. An acute high dose of uranyl nitrate also delayed both tooth eruption and development in rats [P33]. However, the retardation observed seven days after acute uranyl nitrate exposure was reversed completely after 27 days [P34].

137. The in vivo results were confirmed by in vitro studies that showed that human osteoblasts were sensitive to uranium effects (increased reactive oxygen species production, decreased alkaline phosphatase activity, modified osteoblast phenotypes, genomic instability) [M38, M39, M42, T3]. An increase in oxidant stress shown by an increased lipid peroxidation was also observed in vivo in rat bone at high doses [G8].

2. Chronic exposure

138. On the basis of measured tissue concentrations and organ weights [F4, F8, L22, W26], bone tissue may contain up to 66–75% of the body burden of uranium following chronic exposure to uranium.

139. Several rat studies were designed to determine the uranium content of bones following chronic contamination [A24, P3, R18]. Rodrigues et al. showed that accumulation of uranium in the rat skeleton following intake via food increased to reach a plateau after one month [R18]. A long-term study of Paquet et al. demonstrated that uranium accumulation in bones increased until 18 months [P3].

140. Some experiments investigated the long-term accumulation in bones of young male rats (between the weaning and the post-puberty periods) [A23, R18]. Experiments performed on females during the growing period indicate that concentration of uranium in the animals' femora increased faster in the early stages of the animal life, then saturating in adult animals.

141. Contamination of growing rats with uranium in food led to accumulation in bones (0.1–1.1 µg U/g bone) that exhibited the same pattern as the skeleton growing curve. Despite this accumulation, there was no change in the bone mineral density (BMD) [R18]. However, uranium exposure of adults led to a decrease in the BMD.

142. In contrast, a study of chronic exposure of growing rats to natural uranium for nine months via daily oral ingestion (uranium-contaminated drinking water at 40 mg/L) affected the skeleton by decreasing messenger RNA (mRNA) expression of genes involved in bone metabolism and decreasing femoral cortical bone area, while no changes were observed in adult rats [W1]. Chronic contamination by subcutaneous implantation of powdered uranium dioxide (125 mg/kg) in rats resulted in an inhibition of bone formation as has also been described for acute poisoning with uranium [D15].

143. Bone metabolism was investigated in human populations receiving high levels of uranium via drinking water by measurements of biochemical indicators of bone formation (osteocalcin and amino terminal propeptide of type I procollagen) and a marker for bone resorption (serum type I collagen carboxy-terminal telopeptide (CTx)) [K27]. The authors showed an elevation of CTx and osteocalcin that could be associated with increased uranium exposure.

3. In vitro studies: mechanisms

144. The cytotoxic effect of uranium on rat and human osteoblasts is highly dependent on its speciation. Exposure to non-toxic doses or non-toxic species of uranium induces the activation of two markers of bone formation and mineralization (osteocalcin and bone sialoprotein), while their inhibition is observed after toxic exposure [M37, M38]. This study highlights the importance of a controlled speciation of uranium in toxicological studies.

145. In vitro transcriptomic studies performed on several human cell lines taken from kidneys or lungs as representative targets have highlighted the involvement of osteopontin in the uranyl toxicity mechanisms [P29]. This major non-collagenous protein involved in the organo-mineral homeostasis of the bone presents a specific composition in acidic clusters associated with numerous phosphorylations, and also a relative plasticity. Qi et al. showed with in vitro models that native phosphorylated osteopontin binds uranyl with a nanomolar affinity and that this binding induces conformational changes enabling the formation of a very stable complex of uranium [Q1].

4. Conclusion

146. In conclusion, acute and chronic exposure to uranium-induced biological effects on bone metabolism such as the impairment of bone growth and of bone formation and the inhibition of endochondral ossification or the delay of development. Most effects were observed in experimental models (rodents or isolated humans cells). One study performed on humans exposed to high levels of uranium in drinking water showed an elevation of type 1 collagen carboxy-terminal telopeptide (CTx), a plasma marker for bone resorption, and of osteocalcin, indicator of bone formation [K27]. All these studies—in animals and humans—suggest that uranium affects bone turnover. Osteoblasts appeared to be the main cell targets of uranium. Some effects were also observed in humans, indicating that bone may be a target of uranium chemical toxicity in humans.

D. Lungs

1. Acute exposure

147. In general, the more soluble compounds (uranyl fluoride, uranium tetrachloride, uranyl nitrate) are less toxic to the lungs but more toxic to distal organs due to easier absorption of the uranium from the lungs into the blood and systemic transport [G1].

148. The behaviour of uranium in the lungs following inhalation has been studied in animal experiments from various industrial settings [A31, C30, C31, D3, E3, S35, S38, S39, S40, W19, W20]. These studies demonstrated that the behaviour of uranium, its distribution, and its clearance in lungs is dependent on the solubility of uranium compounds. Results of these experiments were used to confirm or improve the ICRP models as described in chapter V on biokinetics.

149. Concerning the clinical effects of uranium in the respiratory system, authors reported alveolar fibrosis in rats [M60], congestion and haemorrhage in rats and guinea pigs [L19] and bronchopneumonia in rats and rabbits [D36] for uranium levels of between 10 and 100 mg/m^3. The comparison of repeated and acute uranium exposure via inhalation was performed in rats [M55] with aerosols varying from 116 to 375 mg/m^3. The results showed that UO_2 repeated pre-exposure by inhalation increased the genotoxic effects of UO_4 inhalation, when UO_4 exposure alone had no effect. However, it is not clear if these effects were due to a potentiation of the effect of UO_4 by pre-treatment with UO_2 or to a cumulative effect of the two types of exposure.

2. Chronic exposure

150. Experimental studies performed on dogs, monkeys and rats with uranium show that inhalation of natural uranium dioxide (UO_2) at a mean concentration of 5 mg U/m^3 for periods as long as five years led to pulmonary neoplasia and fibrosis [L18]. Pulmonary neoplasia developed in a high percentage of the dogs examined two–six years after exposure. Pulmonary and tracheobronchial lymph node fibrosis, consistent with radiation effects, was dose dependent and more marked in monkeys than in dogs.

151. Nose only inhalation in rats showed that chronic inhalation of natural uranium ore dust (without significant radon content) created a risk of primary malignant and non-malignant lung tumour formation [M49]. The frequency of primary malignant lung tumours was 0.016, 0.175 and 0.328 and primary non-malignant lung tumours 0.016, 0.135 and 0.131 in the control, low (19 mg/m^3 leading to an absorbed dose of 0.87 Gy) and high (50 mg/m^3 leading to an absorbed dose of 1.64 Gy) aerosol exposed groups, respectively, without difference in tumour latency between the groups. Despite lymph node specific burdens ranging from 1 to 60-fold greater than the specific lung burden in the same animal, no lymph node tumours were observed.

3. In vitro studies: mechanisms

152. Inhalation of soluble uranyl nitrate led to uranium uptake in the lysosomes of alveolar macrophages and precipitation in the form of insoluble phosphate [B20]. A study by Lizon and Fritsch on alveolar macrophages with uranium concentrations from 5×10^{-5} to 10^{-3} M showed that the toxicity of uranium was concomitant with the presence of insoluble forms in the culture medium [L40].

153. Orona and Tasat analysed rat alveolar macrophages to better understand the pathological effects associated with DU inhalation, metabolic activity, phagocytosis, genotoxicity and inflammation [O6]. The effects of 12.5–200 μM DU seemed to be dose-dependent, most observed from 100 μM. At low doses, DU induced phagocytosis and at high doses, provoked the secretion of TNFα. Apoptosis was induced through the whole range of doses tested. The uranium-induced TNFα secretion by macrophages was consistent with results from previous studies [G5, Z11]. Lung fibrosis was correlated with abnormal expression of TNFα and IL−6, which could be antagonized by antibodies against TNFα [Z11, Z12].

154. Orona and Tasat suggested that at low doses (12.5 μM), DU induced O_2^-, which may act as the principal mediator of DNA damage, while at higher doses (200 μM), the signalling pathway mediated by O_2^- may be blocked, and the prevailing DNA damage would be by TNFα [O6]. A study by Monleau et al. indicated that exposure to DU by inhalation resulted in DNA strand breaks in broncho-alveolar lavage cells and in an increase in inflammatory cytokine expression and production of hydroperoxides in lung tissue [M56].

155. In addition to effects on pulmonary macrophages, a study showed that uranium (from 0.25 to 1 mM) induced significant oxidative stress in rat lung epithelial cells followed by a concomitant decrease in the antioxidant potential (glutathione and superoxide dismutase) of the cells [P13]. Further, some publications indicated that not only soluble (uranium acetate) but also particulate (uranium trioxide) uranium induced concentration-dependent cytotoxicity in human epithelial cells [W22].

156. Depleted uranium was clastogenic and induced chromosomal aberrations after 48 hours [L4]. Xie et al. [X1] found a loss of contact inhibition of these cells after particulate DU exposure, with chromosome instability and a change of cell phenotype, suggesting a neoplastic process.

4. Conclusion

157. Experimental acute and chronic studies demonstrated possible effects of uranium on fibrosis and tumour formation in lungs. Data obtained in vitro indicated the induction of genotoxic lesions (DNA strand breaks) and activation of inflammatory pathways on alveolar macrophages with high uranium concentrations. However, these underlying mechanisms were not investigated in vivo, limiting the relevance of these molecular effects to understand the link between uranium exposure and observed pathologies (fibrosis and tumour formation).

E. Liver

158. Accumulation of uranium was observed in the liver of rats after injection, implantation or oral administration (uranyl nitrate) but at a lower concentration than in the kidneys for the same level of exposure [C35, P3, P11]. Acute exposure led to decreased liver weight and increased plasma transaminase levels, both indicators of liver hepatotoxicity in rats [G24, M57, O7] and in mice [O11].

159. More recently, some results were published on hepatic effects of uranium following in vivo exposure of rats [D29, G29], which demonstrated that some enzymes of xenobiotic metabolism, notably the cytochrome P450 of type 3A (CYP3A), were modified by chronic contamination with DU. The time-course study performed at 1, 3, 6, 9 and 18 months after exposure indicated that significant changes were observed at six and nine months [G29], with a 50% decrease in the mRNA level of

CYP2C11 at six months and an increase in gene expression of CYP3A at nine months. Concerning the dose–response study, the most substantial effects were observed in the liver of rats after nine months of exposure to 120 mg/L: CYP3A gene and protein expression and enzyme activity all decreased by more than 40% [D29, G29].

160. Several studies investigated the functional consequences of a co-exposure to uranium (uranyl nitrate) and the drugs chlorzoxazone [C26, M57], ipriflavone [C25], theophylline [Y4] or paracetamol [G27, R25] in rats. Altered drug pharmacokinetics was observed with high dose and chronic low dose exposure to uranium, which could be due to liver dysfunction. Functional toxicity of uranium was also estimated by measuring xenobiotic detoxification enzymes and their gene expression levels, protein levels or enzyme activities. Some studies reported altered levels of xenobiotic detoxification enzymes [G27, P6] while others reported altered pharmacokinetic metabolism of certain drugs after acute [C25, C26, M57] and chronic exposure to uranium [G27]. Oxidative stress may also occur in hepatocytes exposed to uranium, as demonstrated by mitochondrial or lysosomal alterations [P26] or metallothionein involvement [M47].

161. Chronic contamination with DU (uranyl nitrate, 1 mg/rat/day for 9 months) affected cholesterol metabolism in the rat liver [R2]. Relative mRNA levels of the enzyme cholesterol storage were modified, and also the proteins involved in the transport and the regulation of cholesterol homeostasis. One accident involving workers with extensive skin exposure to uranium has been reported in the literature [L48, S16, S49]. These results were similar to observations from the clinical follow-up of workers with acute uranium compound intoxication. Toxic hepatitis occurred for several days post-accident with recovery one month later [S16]. The result of 33-year follow-up showed that liver functions were normal [S49]. In conclusion, experimental studies performed in rats indicated that uranium exposure induced some biological effects on the liver, without a high uranium accumulation in this organ. These biological effects did not lead to the appearance of pathologies in animals. However, in humans, one study reported a transient toxic hepatitis.

F. Brain

1. Behavioural effects

162. Adult rats exposed to uranium showed subtle but significant behavioural changes. Increases in locomotor activity, in line crossing and in rearing behaviour were observed after exposure of rats to DU in drinking water at 2 or 4 mg/kg per day or after inhalation [B52, M54]. Females seemed to be more resistant: unlike males, they did not show locomotor symptoms [B51]. Exposure to uranium to 0.1, 0.3 or 1 mg uranium/kg also affected working memory with poorer performance (decreased latency) in a light–dark passive avoidance response system [B6]. The spatial working memory measured by the percentage of spontaneous alternation was significantly lower after exposure to DU by inhalation and after ingestion of 1 mg per day of 4% enriched uranium [H24, H25, M54]. Lastly, exposure at this dose of enriched uranium had a deleterious effect on anxiety and increased the amount of rapid eye movement in sleep [H24, H25, H26]. However, DU had no significant effect in the same experimental conditions [H24, H26, L30]. A recent review summarized the different effects of uranium on behaviour. It can lead to neurobehavioural impairments, including increased locomotor activity, perturbation of the sleep-wake cycle, decreased memory, and increased anxiety. The mechanisms underlying these neurobehavioural disturbances are not clearly understood [D16].

163. Mouse experiments were conducted on ApoE$^{-/-}$ mice that had been genetically knocked out for the apolipoprotein E gene, the product of which regulated cholesterol metabolism. These mice had hypercholesterolemia and expressed biochemical markers of Alzheimer's disease. Administration of DU to these mice resulted in impaired memory compared to unexposed ApoE$^{-/-}$ mice [L33]. This cognitive effect was associated with a trend toward higher total cholesterol content in the cerebral cortex (+15%). This study demonstrated that some pathological conditions may increase sensitivity to uranium. Table 12 summarizes the main studies on animal behaviour after uranium exposure.

Table 12. Summary of studies of uranium exposure on rodent behaviour

im: intramuscular; DU: depleted uranium; EU: enriched uranium

Uranium compound	*Species*	*Exposure conditions*	*Main biological effects*	*Reference*
Uranyl acetate	Adult rat	2 and 4 mg/kg/day (water) DU during 2 weeks and 6 months	Increased locomotor activity	[B52]
Uranyl nitrate	Adult rat	2.5, 5 and 10 mg/kg/day (water) DU during 3 months	Increased locomotor activity, decreased spatial memory	[B11]
Uranyl dioxide	Adult rat	Inhalation DU 30 min at 197 mg/m^3, 4 days a week for 3 weeks	Increased locomotor activity and decreased spatial memory one day post-exposure	[M54]
Uranyl acetate	Adult rat	im. 0.1, 0.3 and 1 mg/kg DU	Decreased locomotor activity, decreased grip strength, decreased working memory at 6, 13, 20 and 27 days post-dosing	[B6]
Uranyl nitrate	Adult rat	1 mg/kg/day (water) 4% enriched uranium (EU) during 1.5 months	Decreased spatial memory, increased of anxiety	[H25]
Uranyl nitrate	Adult rat	1 mg/kg/day (water) 4% EU during 1.5 months	Increased paradoxical sleep	[L29]
Uranyl nitrate	Adult rat	i.p. 144 µg /kg 1 and 3 days	No change in sleep-wake cycle	[L30]
Uranyl nitrate	Adult rat	1 mg/kg/day (water) 4% EU during 3 or 9 months	Decreased spatial memory	[H24]
Uranyl acetate	Fetal mouse	1, 2 and 4 mg/kg/day DU during gestation and lactation	Accelerated appearance righting reflex, forelimb placing, grasping, swimming and weight gain	[B50]
Uranyl acetate	Young mouse	1, 2 and 4 mg/kg/day (water) DU during 21 days since the birth	Decreased locomotor activity, decreased working memory	[B51]
Uranyl acetate	Fetal rat	10, 20 and 40 mg/kg/day (water) DU during 3 months (male)	Decreased learning in pups	[A10]
Uranyl nitrate	Adult rat	1 mg/kg/day (water) DU during 2 months since the birth	Decreased spatial memory	[B15]
Uranyl nitrate	Adult mouse (ApoE$^{-/-}$)	4 mg/kg/day (water) DU during 3.5 months	Impaired memory	[L33]

2. Neurotransmitters

164. Several experimental studies suggest that uranium can induce changes in neurotransmitter levels: acetylcholine levels were unchanged in the hippocampus after exposure to 1 mg DU per kg and day but were decreased in the cortex [B14]. Chronic DU contamination induced a fall in the rate of acetylcholine (ACh) and AChE activity in the entorhinal cortex and cerebellum [B15, B55]. This disturbance of cholinergic function was associated with a decrease in gene expression of several proteins [B14]. These studies suggest that the modifications of neurobehavioural tasks following uranium exposure could be linked with a change of AChE activity in the cerebral cortex [B52].

165. A study performed in Sprague-Dawley rats (following 1.5, 6, or 9 months with 2.7 mg U/kg per day) reported that AChE activity was not significantly affected in the striatum, hippocampus, or frontal cortex at any time point, but it was significantly decreased in the cerebellum at six months [B55]. Depleted uranium exposure at 2.7 mg/kg per day also induced a significant decrease in AChE activity in the striatum and cerebral cortex [B14, B55]. A dose–response study performed at nine months following chronic contamination indicated that uranium effects (15% decrease in AChE activity) were independent of uranium content in drinking water (from 0.2 to 120 mg/L).

166. A 1.5-month ingestion of 1 mg U/kg per day increased the dopamine level in the hypothalamus [B55]. Chronic exposure produced a significant decrease in the serotonin (5HIAA) level and the serotoninergic (5HT-ergic) turnover ratio in the frontal cortex and also a decrease in the dopamine (DOPAC) level and dopaminergic (DA-ergic) turnover ratio in the striatum [B55]. It appeared that disruption of these systems differed depending on the brain structure considered, the time of exposure and the degree of uranium enrichment [A1, B14, B55, L29].

3. Oxidative stress

167. One specific mechanism by which uranium leads to neuro-effects could be oxidative stress. The behavioural changes correlated with lipid peroxidation in the brain induced by uranium [B52, G8]. The gene expression or enzymatic activity of the main antioxidant enzymes, i.e. superoxide dismutase, catalase and glutathione peroxidase, increased significantly in the hippocampus and the cerebral cortex after exposure to DU and decreased after exposure to 1 mg of 4% enriched uranium per kg per day [L31, L38]. The cell response to DU could be interpreted as a defensive mechanism towards free radical damage to cerebral tissue (increase of several antioxidant agents in order to counteract the oxidative stress). The oxidative stress induced by the enriched uranium is possibly too high to be counteracted by the cell defences.

168. A dose–response study performed nine months after chronic contamination with DU from 0.2 to 120 mg/L indicated that uranium affected the activity of these enzymes differently (diminution for SOD and increase for GPx or Catalase). The gene expression of inducible nitric oxide synthase, the enzyme that synthesizes nitric oxide, increased significantly after chronic exposure to 1 mg DU per kg and day [L38]. Repeated administration of DU as uranyl acetate during seven days also increased the nitrite levels in the brains of rats [A1].

4. Exposure of developing animals

169. In rodents, exposures at 1, 2 or 4 mg DU/kg per day during development accelerated the appearance of several types of behaviour: righting reflex (for example, when the rat is put on its back, it turns over immediately), placing reactions (for example, the rat is held by the tail over a table until its whiskers get near, when it puts its paws on the table), grasping (the rat is picked up and the palm is touched with a wire and the response is to grip the wire), swimming and weight gain [B50].

170. Animals exposed to uranium at 1, 2 or 4 mg U/kg per day during development had a decreased locomotor activity [B51] and their performance was worse on a test of working memory [B15]. The spatial learning of the offspring of uranium-exposed male rats at 1, 2 or 4 mg U/kg per day for learning was also affected [A10]. A dose–response study (0, 10 or 40 mg/L of uranium in drinking water) indicated no significant uranium effect on behaviour at 10 mg /L, and an impairment of object recognition memory (−20%) at 40 mg/L [L32].

171. Neurogenesis processes during pre- and postnatal brain development were studied in rats by investigating the structural morphology of brain, cell death and cell proliferation after chronic exposure to drinking water contaminated with uranium (40 and 120 mg/L) [L26]. Major changes were observed at 120 mg/L, both during prenatal and postnatal periods. At the highest dose, DU caused opposite effects during brain development on cell proliferation and cell death processes, mainly between prenatal and postnatal development. These modifications did not have a major impact on brain morphology but they could affect the next steps of neurogenesis and disrupt the organization of the neuronal network.

172. Some studies were published on the comparative effects of depleted and enriched uranium in rats [H24, L31]. Chronic exposure to 4% enriched uranium for 1.5 months through drinking water increased the amount of paradoxical sleep, reduced the spatial working memory capacity and increased anxiety while no effect was observed following exposure to DU [H24]. These cognitive effects were associated with imbalance of oxidative stress [L31]. Indeed, lipid peroxidation was increased in brain after enriched uranium exposure but not after DU exposure. Enriched uranium induced a decrease of anti-oxidative enzymes, and DU induced an increase of these anti-oxidative enzymes.

5. Conclusion

173. Animal studies suggest that uranium can have some negative effects on the behaviour of mature animals that could be explained at a neurochemical level (neurotransmitters, oxidative stress) for highest doses. In addition, some results obtained in rats and mice demonstrate differential effects between depleted and enriched uranium, suggesting the importance of the radiological toxicity of uranium. The data also suggest that the developing animal may acquire a specific sensitivity to uranium effects. In humans (workers or public), the correlation between behavioural symptoms and exposure to uranium was not demonstrated. Thus, data obtained in animals are only suggestive until they can be tied to meaningful human research.

G. Reproduction and development

1. Female reproductive function

174. Results for measurements of uranium concentrations in gonads were contradictory depending on the study (species, administration pathway, uranium dose and exposure time). In fact, high uranium accumulation is found in some fish and birds. For instance, significant uranium accumulation was measured in female fish gonads (Danio rerio), corresponding to >20% of the relative burden [S20].

175. A dose-dependence of uranium concentration in ovaries was measured in rats and their offspring after chronic oral exposure via food [H9, H10]. The accumulation of uranium was higher in the second exposed generation. Other experimental studies performed on mice failed to report uranium accumulation in the ovary after contamination by nitrate uranyl with doses up to 400 mg/L for uranium content in drinking water [A21, F2, R9].

176. Some studies found that uranium affected oocyte quality in vivo with a 50% reduction in the proportion of healthy oocytes from 20 mg/L [F2] and germinal vesicle oocytes cultured in vitro in the presence of 1 mM uranyl acetate and observed for 72 hours [A21]. In vivo, these morphological effects were observed from uranium content in drinking water above 5 mg/L [F2]. A study with similar approaches (uranium ingestion via drinking water in mice) indicated similar results, with increased dysmorphism of oocytes in contaminated groups (from 2.5, 5 and 10 mg U/kg per day chronically administered in drinking water for 40 days) in a dose independent manner [K24]. In addition, a study on mice contaminated in utero by uranium levels in drinking water from 0.5 to 60 µg/L, showed an increase in uterine weight and a decrease in primary follicles [R9].

177. Reproductive effects following chronic oral uranium exposure were observed in rats exposed during the first and the second generation [H10]. No effect were observed in F_0 rats, but pregnancy rate, normal labour rate, and survival rate were decreased in offspring [H10]. In vitro organ culture system was used to investigate the effects of uranium on human gonads during the first trimester of gestation (7–12 weeks) [A13]. Uranium at 0.05 mM increased the apoptosis rate, decreasing the germ cell density of human fetal ovaries. The authors also demonstrated that human fetal germ cells were more sensitive to uranium than mouse germ cells.

2. Male reproductive function

178. Some animal studies indicated accumulation of uranium in testes with 0, 5, 10, and 25 mg/kg/day of uranyl acetate dehydrate before mating and up to 21 days post birth [P7]. A linear dose-dependence was found in testes of Japanese quail, with a ratio of accumulation similar in testes and in kidney [K25]. A dose-dependence of uranium concentration in testes was measured in rats and their offspring after chronic oral exposure via food [H10]. The accumulation of uranium was higher in the second generation.

179. Concerning the effects of DU on sex hormone levels, experimental studies performed in male rats showed differing results. One experiment performed in male rats indicated an increase in testosterone and luteinizing hormone levels and a decrease in follicle stimulating hormone level after a four-month contaminated food ingestion [H10], while a nine-month contaminated drinking water ingestion did not lead to changes in testosterone and 17β-estradiol levels [G20]. The different uranium doses 4 and 40 mg/kg per day in the studies of Hao et al. [H10], and 2.7 mg/kg per day in the study of Grignard et al. [G20] were used to explain the different levels. However, changes in testosterone levels were not

observed in depleted-uranium Gulf War veterans [M19, M20]. A nine-month chronic oral exposure to enriched uranium produced a significant increase in the blood levels of testosterone at 40 mg/L in drinking water, while no effect was observed with DU [G20].

180. Some reports on rodents highlighted a negative impact of uranium on male reproductive function, including a decrease in male fertility and in the spermatid number per testis with a few histopathological effects on the seminiferous tubules and interstitium after chronic exposure [L37, L41]. Although some abnormal morphological forms and sperm parameters measured were affected by uranium exposure, these changes were independent of the uranium dose levels from 10 to 40 mg/kg per day corresponding to ~200 to 800 mg/L in drinking water, respectively [L37]. Further, a dose-independent decrease in the pregnancy rate was observed in untreated females mated with male mice exposed to between 10 and 80 mg/kg per day of uranium [L41].

181. Implantation of DU pellets did not change the concentration, motion and velocity of sperm, and there is no evidence of detrimental effects of uranium on mating success, suggesting that implantation of up to 20 DU pellets of 1×2 mm (760 mg) in rats did not have an adverse impact on male reproductive success, sperm concentration, or sperm velocity [A19]. Testicular histopathological abnormalities with deformations of seminiferous tubules (marked reduction in the seminiferous tubule diameter) were observed in mice after high acute exposure [J1]. A seven-day daily intraperitoneal administration of uranyl nitrate (0.5 mM/kg) induced a marked reduction in the seminiferous tubule diameter and gametogenic count, with signs of testicular necrosis and exfoliation of germ cells, including karyolysis and karyorrhexis figures.

182. The contribution of new in vitro models, such as organotypic culture systems, helps the understanding of the underlying action mechanism of chemicals. This approach was used as a toxicological test to evaluate the effects of various compounds, including uranium, on gametogenesis and steroidogenesis in rat, mouse and human testes [H1]. Some effects on germ cell development (reduction of the number of germ cells) or Leydig cell function were observed for uranium concentrations above 5×10^{-5} M in human testis cells and above 5×10^{-4} M in rat testis cells [A13].

183. Uranyl fluoride injected in vivo into mouse testes led to an increase in the frequency of chromosomal aberrations in spermatogonia and primary spermatocytes [H27]. These results were confirmed in another study that indicated the highest effects when doses of UO_2F_2 increased up to 6 mg/kg at 12 days post-exposure [H28]. A study performed with enriched uranium demonstrated chromosome aberrations in spermatogonia [Z15]. Chromosome fragmentation, translocation, polyvalence in primary spermatocyte and DNA strand breakage were observed in sperm. Effects of uranium on human male reproduction studied in Gulf War I veterans did not evidence deleterious effects on sperm quality, including volume, concentration, total sperm count, and functional parameters of sperm motility [M20, M21, M22].

3. Effects on embryos and development

184. The effects of uranium on embryotoxicity were studied in rats and mice after acute exposure [D17]. Subcutaneous injections of uranyl acetate dihydrate (0.5, 1 and 2 mg/kg/day) in mice from day 6 to day 15 of gestation induced various effects [B44]. Although it was not dose-related, embryo-toxicity also occurred in all uranium-treated groups (significant increases in the number of non-viable implantations and in the percentage of postimplantation loss). Both the maternal NOAEL and the NOAEL for embryotoxicity of uranyl acetate dihydrate were below 0.5 mg/kg/day, whereas the NOAEL for teratogenicity was equal to 0.5 mg/kg/day.

185. Few animal studies investigated the effects of uranium exposure on development and results were conflicting, depending on the quantity of administrated uranium and the exposure duration. Subcutaneous injections of uranyl acetate dihydrate from day 6 to day 15 of gestation induced malformations detected at 1 and 2 mg/kg/day in mice [B44], while no effect was observed at 0.5 mg/kg/day.

186. Paternain et al. demonstrated that embryo lethality could be observed in mice contaminated at 25 mg/kg/day [P7]. Significant increases in the number of dead young per litter were seen at birth and at day 4 of lactation in the 25 mg/kg/day group. The growth of the offspring was always significantly lower for the uranium-treated animals. Since no effect was observed at lower doses (5 and 10 mg/kg/day), the results suggest that uranium does not cause adverse effects on fertility, general reproductive parameters, or offspring survival at the concentrations usually ingested by man.

187. In vitro studies were also conducted on one-cell mouse embryos in culture medium with uranyl nitrate at concentrations of 26, 52, 104 and 208 µg/mL [K23]. The results obtained showed that concentrations from 26 µg U/mL induced the delay of embryo development and the impairment of blastomere proliferation. A study of acute toxicity was performed in mice receiving 4 mg/kg of DU per intraperitoneal injections (i.p.) at day 11 of gestation and observations were made 4 days later. Paradoxically, the authors found an increase in the fetus length and weight [M46].

188. Subcutaneous injections of uranyl acetate (0.415 and 0.830 mg/kg/day) were given to pregnant rats on days 6 to 15 of gestation [A9]. Maternal toxicity and embryotoxicity were noted at the higher dose, while fetotoxicity was evidenced at both doses. The fetotoxicity was evidenced by significant reductions in fetal body weight and increases in the total number of skeletal abnormalities [A9].

189. Some studies indicated developmental toxicity of uranium, including teratogenicity, following an acute subcutaneous administration of 1 or 2 mg/kg/day [B44, D18]. A study by Zhu et al. [Z15] was performed with enriched uranium injected in rat testes, causing skeletal abnormalities in fetal rats with a positive correlation to the injected dose.

190. Hereditary effects of uranium were investigated in rats following the implantation of uranium pellets in muscle (up to 12 DU pellets corresponding to 360 mg) [A20]. This study indicated no changes in sperm motility and ribcage malformations, suggesting that uranium was not a significant reproductive or developmental hazard. This study is in accordance with another study that indicated that uranium did not cause any adverse effects on fertility, general reproductive parameters, or offspring survival at the concentrations usually ingested by humans [P7]. One study performed on mice investigated the transmission of genetic damage to offspring of fathers contaminated with uranium via depleted-uranium-implanted pellets [M45]. The authors demonstrated a dose-dependent increase in mutation frequency in the offspring. Congenital malformations [A6, A7, S48] or birth defects [A3, B54, F1] were reported in some human populations, but these effects were not correlated to a quantification of uranium exposure.

4. Conclusion

191. Some publications focused on reproduction and development issues after exposure to uranium in animals (rats and mice). These studies indicated that both male and female reproductive functions (quality of oocytes and sperm parameters, embryo viability, and the development processes) may be affected by acute and chronic exposure. However, these effects were observed for exposure levels greater than either typical occupational or environmental levels of exposure.

H. Other organs

1. Skin

192. A study of acute exposure of rabbits was conducted using different administrations of uranium oxide: subcutaneous deposit of ~30 mg U_3O_8; cutaneous deposit of 70 mg of U_3O_8 or 5 µg of uranium acetate (1.9 kBq of ^{233}U) [W3]. Uranyl nitrate, in ethereal or aqueous solution, produced a superficial coagulation necrosis within a few hours [O4]. A similar but delayed effect was seen seven–nine days following the application of powdered hygroscopic uranium pentachloride to the skin. Uranium tetrachloride in suspension in lanolin caused a moderate local erythema of the skin at the site of application, which disappeared in one–two days.

193. In vitro studies on primary cultures of rat skin keratinocytes and fibroblasts [P15] showed a greater decrease in proliferation rate associated with a greater mortality rate in rat skin keratinocytes than in rat skin fibroblasts after uranium exposure. This can be explained by the three times higher ability of keratinocytes to incorporate uranium compared to fibroblasts. This greater capacity of epidermal cells than dermal cells to incorporate uranium was confirmed in vivo in hairless rats following topical contamination with uranyl nitrate.

194. The consequences of protracted exposure to uranium were investigated using guinea pigs and rabbits [O4]. Guinea pigs that were repeatedly exposed to uranyl nitrate exhibited a superficial coagulation necrosis and an inflammation of the epidermis. Their skin was in a constant state of encrustation and desquamation accompanied by rapid regeneration from beneath. Rabbits that were repeatedly exposed at multiple dermal sites exhibited an effect similar to that seen after single acute exposure, but those rabbits that were repeatedly exposed at the same site developed severe dermal ulcers after five to ten applications of the compound. Another in vivo study in rats revealed that long-term exposure of the dermis to uranium (U_3O_8 at 0.012 g/d for 30 daily topical applications) led to an epidermal atrophy which, in turn, resulted in an increased permeability of the skin [U2].

2. Endocrine system and metabolism

195. Vitamin D is essential for the homeostasis of calcium and phosphorus in the body. A few studies have determined the effects of acute or chronic uranium contamination on the metabolism of vitamin D in rats. Contamination by DU via drinking water at 40 mg/L [T11] induced a decrease in the blood levels of vitamin D in rats following a nine-month chronic exposure. Moreover, uranium targeted key transcription factors (PPARα, PPARγ, HNF-1α, HNF-4α, LXRr, RXRα, and VDR) involved in this metabolism [T11, T12]. However, these molecular changes did not lead to the emergence of disease associated with vitamin D metabolism.

196. Chronic contamination by DU (uranyl nitrate, 2.7 mg/kg/day for 9 months) affected cholesterol metabolism in the liver and brain [R1, R2], mRNA levels of the enzymes involved in the cholesterol storage were modified in the liver and brain, and mRNA levels of enzyme involved in the cholesterol synthesis were modified in the brain. Uranium also affected the proteins involved in the transport of cholesterol and the regulation of cholesterol homeostasis. Thus, a chronic ingestion of uranium

(40 mg/L in drinking water) caused subtle molecular effects on metabolism in the liver and brain of rats. However, overall cholesterol levels were unaltered in this study using 40 mg/L uranium in drinking water.

197. Studies of rats exposed to uranium showed both disruptive effects on the reproductive system and estrogenic effects. Chronic contamination with DU (560 Bq/L) in drinking water produced no change in the blood levels of the two principal steroid hormones—oestradiol and 17β-testosterone (synthesized by the testis), whereas contamination with enriched uranium (1,680 Bq/L; 40 mg/L) produced a significant increase in the blood levels of testosterone [G20]. Consistent with the absence of hormonal changes with DU, chronic contamination with DU did not induce a change of gene expression. However, the expression of enzymes involved in the metabolism of hormones was amplified following a nine-month exposure to enriched uranium. In addition, enriched uranium increased the gene expression of transcription factors (RXR, LXR, FXR, SHP, SF-1, DAX-1) that positively regulate steroid metabolism. These results show a differential effect of depleted and enriched uranium contamination on testicular steroidogenesis [G20].

198. The human body is frequently exposed to potentially toxic compounds and is able to metabolize them in order to protect itself. Xenobiotic-metabolizing enzymes, including cytochrome P450 (CYP450), play a central role [G25]. The kidneys and liver can metabolize many drugs or other xenobiotics. Disturbances of this system have been demonstrated in vitro [M43] and in rats exposed to nephrotoxic [M57] or non-nephrotoxic uranium concentrations [P6, S29]. These studies showed that the expression and activity of CYP450 can be modified by uranium exposure. The consequences of such modifications on xenobiotic metabolism were investigated using acetaminophen [G26]. Rats contaminated with DU presented slower plasma acetaminophen elimination and also more marked renal histological changes and an increase in blood markers of liver damage (at 40 mg/L during 9 months). However, only slight effects of uranium were reported on enzymes of xenobiotic metabolism when acetaminophen was administrated to rats as a single therapeutic treatment [R25].

199. In conclusion, studies performed on animal models (rat and mouse) chronically exposed to radionuclides showed that the chronic ingestion of uranium resulted in subtle biological effects on various metabolic systems. These modifications did not lead to the appearance of pathologies, even for uranium levels in drinking water up to 40 mg/L. The observed biological effects probably resulted from an adaptive response to the internal contamination.

3. Immune and haematopoietic systems

200. Very few studies have investigated the effects of uranium exposure on the haematological system. Reduced erythropoiesis might be expected owing to accumulation of uranium in bone in proximity to bone marrow and renal damage might result in a decrease in the number of red blood cells. A study using rats found that chronic ingestion of uranium at 40 mg/L in drinking water for nine months led to kidney deterioration which may have been responsible for an observed decrease in the red blood cell count; there was an associated modification of spleen erythropoiesis and levels of molecules involved in erythrocyte degradation [B19].

201. A study by Giglio et al. was performed to assess the effect of uranium (uranyl nitrate) on the rate of erythropoiesis in rats [G9]. The authors showed that a single injection of uranium at 1 mg/kg induced a transient depression of the red cell volume between 7 and 14 days. These effects were associated with a decreased Epo production and direct or indirect damage of erythroid progenitor cells.

202. An experimental study using mice fed uranium-contaminated food [H11] compared the effect of concentrations of DU of 0, 3, 30 and 300 mg/kg feed for a duration of four months. The most significant effects were observed in the 300 mg/kg group while the effects were either minor or indiscernible in the other groups. At high dose, the authors observed decreased immune function, manifesting as decreased secretion of inflammatory mediators in the peritoneal macrophages, and also reduced cytotoxicity of the splenic natural killer cells. Moreover, the cellular and humoral immune functions were abnormal (decreased proliferation of the splenic T cells, proportion of the cluster of differentiation (CD) 3^+ cells, ratio of $CD4^+/CD8^+$ cells and delayed-type hypersensitivity, and increased proliferation of the splenic B cells, total serum immunoglobin (Ig) G and IgE, and proportion of splenic $mIgM^+mIgD^+$ cells). The authors concluded that chronic intake of high doses of DU (300 mg/kg) had a significant impact on the immune function, most likely due to an imbalance in T helper Th1 and Th2 cytokines.

203. Studies on rats have addressed the effects of uranium exposure on the mucosal immune system of the intestine following ingestion of uranium-contaminated drinking water [D26, D27, D28]) and in lungs following inhalation [M54, M56, P6]. Studies performed on the rat intestine found that Peyer's patches (aggregated structures of gut-associated lymphoid tissue) were a site of retention of uranium following chronic ingestion (with uranium content in drinking water of 40 mg/L) after 9 months, without inducing any biological effects on the function of Peyer's patches [D26]. However, chronic ingestion of uranium (nine months at 40 mg/L in drinking water) led, in the long term, to some changes in the immune cell populations in lamina propria, diffuse gut-associated lymphoid tissue, notably increase in neutrophil number (+300%) and decrease in macrophage (−50%), and mast cell number (−30%) in rats [D28].

204. Dublineau et al. indicated that immune cell populations in the intestine (neutrophils, mast cells, macrophages) did not vary after 9 months of uranium exposure in rats, at any exposure level (from 0.2 to 120 mg/L in drinking water) [D29]. The authors observed an increase in mRNA levels of cytokines (IFN-gamma, IL-10, and CCL-2), at uranium levels in drinking water >20 mg/L, and a decreased protein expression of cytokines (IFN-gamma, IL-10, and TNFα). Such effects may be explained by uranium interaction with proteasome [M6]. Changes in immune cell populations of the intestinal wall were not reported in the short term following acute contamination with a sublethal dose of uranium in rats (204 mg/kg of DU *per os*) [D27].

205. Immunological changes of long-term uranium exposure were investigated in mice fed with various DU doses (0, 3, 30 and 300 mg/kg food) [H11]. A four-month contamination of animals with 300 mg U/kg food led to a decreased secretion of nitric oxide, interleukin (IL)-1β, IL-18, and tumour necrosis factor (TNF)-α by the peritoneal macrophages, a decreased proliferation of the splenic T cells and increased proliferation of the splenic B cells associated with an increase in total serum immunoglobin (Ig) G and IgE, and proportion of splenic mIgM(+)mIgD(+) cells. Such effects were not observed for the lowest groups (3 and 30 mg U/kg food).

206. Some studies reported effects of uranium exposure on pulmonary immune cells following inhalation in rats [M54, M56, P6]. An uptake of uranium by pulmonary macrophages was found (phagocytosis), followed by an accumulation of uranium in lysosomes [B20, M61]. This accumulation was associated with release of pro- and anti-inflammatory cytokines in vivo [M54, M56] or in vitro [G5, W8, Z12]. Inflammatory cells were observed in proximity to aggregates of uranium particulates [L9]. This inflammatory cell response may lead to oedema and bronchial inflammation [B8, M59]. An induction of apoptosis was observed in vitro in macrophages and T lymphocytes ($CD4^+$) [W8].

207. In the follow-up of United States veterans of the first Gulf War published by McDiarmid et al. [M25], the authors reported for the first time on the analysis of immune function in Gulf War I veterans

exposed to DU, investigating the lymphocyte response to stimulation by two T-cell mitogens. The results on released cytokines (IFNγ, IL-10 and IL-2) in the high- and low-uranium exposure groups did not provide evidence of an effect of uranium on the immune cells.

208. Haematological parameters were recorded in some human populations exposed to uranium. Haematocrit, haemoglobin and RBC content from uranium processing site workers remained within the normal ranges [S10]. Haemoglobin concentrations, erythrocyte counts, haematocrit values, and mean corpuscular volumes were determined on a group of miners in a uranium mine [V6]. There were small differences of mean values from those of controls, such as diminution of haemoglobin concentrations and erythrocyte counts when uranium exposure time increased, but the mean values remained within normal limits. A clinical study of Gulf War veterans showed that soldiers exposed to uranium had a reduction in haemoglobin and haematocrit levels [S32].

209. In conclusion, it appears that slight modifications of the immune system, either systemic or mucosal (including intestines and lungs), were induced following uranium exposure only at high doses, at concentrations usually not incorporated by humans.

4. Cardiovascular system

210. Few human data are available concerning uranium effects on the cardiovascular system. A study was performed on people who had used drinking water from drilled wells containing high levels of uranium (up to 1,500 µg/L) for several years. This study suggested that uranium exposure was associated with greater diastolic and systolic blood pressure [K28]. Two other studies were performed among residents living near the Fernald Feed Materials Production Center, which functioned as a uranium processing facility from 1951 to 1989 [P22, W2]. The systolic and diastolic mean blood pressure levels were higher for population groups living near this uranium plant than those found in the general population, and for most age- and sex-specific groups. However, neither distance nor direction from the site influenced the blood pressure measurement results, suggesting that these findings are not exposure-related [P22]. Another study showed similar results: women with higher uranium exposure had elevated systolic blood pressure compared to women with lower exposure, but the changes observed in diastolic blood pressure or hypertension were not related to exposure level [W2].

211. Concerning experimental studies, there is a lack of literature on the effect of uranium exposure on the development of cardiovascular diseases. One of the consequences of uranium-induced kidney disease could be adverse effects on the cardiovascular systems by a number of mechanisms, including changes to the renin-angiotensin pathway. Several publications have focused on the relationship between kidney and cardiovascular systems in humans [P1, R21, T2]. Consequently, the absence of relevant publications precludes demonstration of an obvious link between uranium exposure and induction of cardiovascular pathologies.

5. Effects on DNA

212. Uranyl acetate staining of DNA has been used for staining fixed cells for more than forty years [H27]. In vitro studies performed with purified DNA showed the presence of a tight binding site for the uranyl ion (UO_2^{2+}) in a four-way DNA junction [M53], demonstrating that uranium can be bound to DNA in vitro. Exposure to uranium may lead to inhibition of DNA-binding proteins [H15, V7]. In vitro studies demonstrated that uranium can displace transcription factor binding to DNA and that it can bind to serum proteins accumulation in the nucleus of human cells [H15, V7]. Experimental studies have

shown accumulation of uranium in the nucleus of human cells (renal, hepatic, neuronal cells) treated in vitro [G30, R26] and in kidney cells of rats treated in vivo [H23].

213. Depleted uranium can induce oxidative DNA damage [B3, K2, M40]. These studies suggested that DU could induce DNA lesions through interaction with cellular oxygen species. These results were corroborated by an in vivo study that showed that inhalation of DU resulted in a production of hydroperoxides in lung tissue of rats [M56]. A recent in vitro experimental study reported the formation of uranium–DNA adducts and mutations in mammalian cells after direct exposure to a compound of DU [S34]. The data suggest that uranium could be chemically genotoxic and mutagenic. The unique mutation spectrum in hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus elicited by exposure to DU suggests that uranium-generated mutations in ways that are different from spontaneous, free radical and radiological mechanisms [C33].

214. Another study on rats demonstrated that UO_2 repeated pre-exposure by inhalation increased DNA single-strand breaks induced by a single UO_4 inhalation exposure in epithelial nasal cells, broncho-alveolar lavage cells and kidney cells, whereas a single inhalation exposure to UO_4 alone had no such effect [M55]. In vitro studies indicated that uranium-induced DNA single-strand breaks were catalysed in the presence of ultraviolet light or ascorbate [M53, N7, Y2]. In vivo [M54, M55] and in vitro [D5, T6] studies showed that uranium induced DNA double-strand breaks. An in vitro study demonstrated that DU was a weak clastogen[2] and induced aneugenic[3] effects while enriched uranium is a more potent clastogen [D5].

215. In summary, experimental studies performed in vivo in rodents or in vitro in cell cultures suggested that uranium could be chemically genotoxic and mutagenic through the formation of strand breaks and covalent uranium-DNA adducts.

6. Cytogenetic damage

216. Uranyl fluoride injected in vivo into mouse testes led to an increase in the frequency of chromosomal aberrations in spermatogonia (breaks and polyploids) and primary spermatocytes (fragments, chromatid exchanges, reciprocal translocations) [H27]. An in vitro study performed on human bronchial fibroblasts indicated no significant increase in chromosomal damage following chronic exposure to uranyl acetate and a slight increase following exposure to uranium trioxide [W22]. An increase in the frequency of sister chromatid exchange and in the frequency of chromosomal aberrations was also observed in cell lines [L36] and in human osteosarcoma cells [M41].

217. A study by Hao et al. using rats showed that chronic oral exposure to DU in food led to an increased frequency of micronuclei in bone marrow cells at 4 and 40 mg U/kg/day in weaning rats [H9]. Miller et al. investigated the transmission of genetic damage to offspring of males mice contaminated with uranium via depleted-uranium-implanted pellets. The authors demonstrated a dose-dependent increase in mutation frequency in the offspring [M45].

218. Chromosome aberrations in Gulf War I veterans following DU exposure were evaluated in several studies [A8, B2, M24, N6]. Four biomarkers of genotoxicity (micronuclei, chromosome aberrations, mutant frequencies of HPRT and PigA[4]) were examined. There were no statistically significant

[2] A clastogen is a mutagenic agent that induces disruption of chromosomes.
[3] An aneugenic agent promotes aneuploidy in cells during mitosis or meiosis leading to the presence of abnormal number of chromosomes in cells.
[4] PigA gene mutation assay is used to assess genomic instability through the measurement of fluorescently labelled antibodies to specific membrane proteins by flow-cytometric methodology.

differences in any outcome measure when results were compared between the low- and the high-uranium groups. However, modelling suggests a possible threshold effect for mutant frequencies occurring in the highest uranium exposed cohort members [M24]. This study demonstrates a relatively weak genotoxic effect of the DU exposure. In the second study [B2], the results indicate that ongoing systemic exposure to DU occurring in Gulf War I veterans with DU embedded fragments does not induce significant increases in micronuclei in peripheral blood lymphocytes compared to micronuclei frequencies in veterans with normal uranium body burdens.

219. Some studies investigated the possible effects of uranium exposure on chromosomal damage in workers and reported an increase in chromosomal aberrations in miners [P25, Z3, Z4] whereas others suggested no significant effects [B49, K21, L42, M33, M70, W25]. Martin et al. performed a study for workers from fuel production and fuel enrichment plants to analyse asymmetrical chromosome aberrations and sister chromatid exchanges [M13]. Both worker groups had higher levels of chromosome aberrations than the studied controls. This effect appeared not to be linked to external radiation. Smoking increased the frequency of dicentrics but not the sister chromatid exchanges in the workers exposed to soluble uranium, suggesting some interaction between the two clastogens.

220. In conclusion, some experimental studies performed on animals or on culture cells at high doses of uranium demonstrate an increase in the frequency of chromosomal aberrations (fragments, chromatid exchanges, reciprocal translocations). Human data are inconclusive but consistent with effects at higher levels of exposure.

7. Tumorigenic potential

221. Information about the carcinogenesis processes induced by uranium in experimental models and humans was provided by the WHO [I5]. Publications on experimental models are detailed below.

222. Chronic inhalation of natural uranium ore dust alone created a risk of primary malignant and non-malignant lung tumour formation in rats [M49]. The risk of the induction of malignant tumours was not directly proportional to dose but was directly proportional to dose rate. A study performed on mice reported an increase in osteosarcoma and acute myeloid leukaemia with ^{239}Pu and ^{241}Am but no significant difference between results for ^{233}U exposed animals and controls [E4]. The authors considered that the observed differences between the radionuclides were due to differences in irradiation of peripheral and central regions of the bone marrow, with lowest doses from ^{233}U. No renal and liver carcinomas were noted [E4].

223. A study by Hahn et al. conducted in vivo showed that intramuscular DU fragments induced soft tissue sarcomas (fibrous histiocytoma, fibrosarcoma and osteosarcoma) at the site of implantation [H3]. However, no direct dose-dependent relationship could be drawn due to the presence of varying corrosion products. Intravenous injection of murine haematopoietic cells into depleted-uranium-implanted mice was followed by the development of leukaemia in 76% of mice implanted with DU pellets in contrast to 12% of control mice [M44].

224. Miller et al. reported the ability of DU-uranyl chloride (10–250 μM) to transform immortalized human osteoblastic cells to the tumorigenic phenotype [M39]. The changes in phenotype are characterized by anchorage-independent growth, tumour formation in nude mice, expression of high levels of the k-ras oncogene, reduced production of the Rb tumour-suppressor protein, and elevated levels of sister chromatid exchanges per cell.

225. Some sparse studies have been performed on DU clean-up workers and on populations from depleted-uranium-contaminated regions [K20, M35, M36]. In clean-up workers, the total number of DNA alterations was higher immediately after decontamination than before decontamination, but tumours did not develop in the group of DU clean-up workers during the investigation period of four years [M36]. This point is not surprising, since four years would be a short latency period for the development of any tumour. In summary, some publications reported tumorigenic effects of uranium in animals (mice or rats) or tumorigenic potential in in vitro models.

I. Relative biological effectiveness

226. Relative biological effectiveness is an empirical value that measures the capacity of a specific type of ionizing radiation to produce a biological effect in a particular biological system (for instance surviving fraction of irradiated cells). It is the ratio of biological effectiveness of one type of ionizing radiation relative to a reference radiation (gamma- or X-rays), given the same amount of absorbed energy. Thus, in the case of uranium isotopes, these values refer exclusively to radiobiological effects of alpha particles compared to the reference radiation. The chemical toxicity of uranium may influence observed RBE values. RBE values are used in experimental radiobiology and are also used by ICRP to derive radiation weighting factors for the calculation of effective dose, which allows the summation of radiation doses for all radiation types for the control of exposure. The value of the weighting factor used by ICRP for alpha particles is 20 compared with a value of 1 for all low-LET radiation [I15]. While there are no direct determinations of alpha particle RBE for uranium isotopes, and such studies would require the use of high specific activity isotopes such as ^{233}U to avoid chemical effects, there is no reason to consider that alpha particles from uranium will have different relative effectiveness from alpha particles of similar energy emitted by other radionuclides (e.g. ^{222}Rn and ^{239}Pu [M12]).

J. Lethal effects

227. The lesion that can cause animal death after acute contamination is tubular nephritis, which, as described above, results from the metallotoxic properties of uranium at high doses. Following intravenous injection of a soluble form of uranium, the lethal dose (LD_{50}) over a period of three weeks after injection was measured as 0.1 mg/kg for rabbits and 20 mg/kg for mice [B20]. In rats, death occurred from 3 to 7 days for doses ≥8 mg/kg [F17]. Following oral ingestion of uranium acetate, the LD_{50} after two weeks was more than 100 mg/kg in rats and mice [D17].

228. One publication reported the deliberate ingestion of uranium (15 g of uranium acetate) [P9]. This ingestion resulted in an acute renal failure, with persistent renal impairment six months after the initial exposure. However, no death was reported despite the high uranium level ingested. This suggested that several grams of uranium for ingestion intakes are necessary for inducing death in humans [K5].

229. As indicated in the recent review of Pernot et al. [P14], the definition and classification of the different types of biomarkers have varied slightly, depending on the biomedical field considered. A biomarker has been defined as “any measurement reflecting an interaction between a biological system and an environmental agent, which may be chemical, physical or biological”. No real bioindicator is specific for uranium exposure. Concerning uranium exposure, the analysis of uranium content (total

concentration or radiological activity in ^{238}U, ^{234}U and ^{235}U) in urine [C18, L21, S37] may provide information on uranium exposure. More indications are given in the uranium measurements section.

230. Since the kidneys are sensitive to damage by uranium, renal molecules were studied to describe potential health consequences [G27, G28]. However, standard potential bioindicators have not yet proven to be sufficiently specific and reproducible. The development and validation of bioindicators that link uranium exposure to renal damage would be valuable [G27].

231. Currently, urinary levels of albumin, glucose, β2-microglobulin and N-acetyl-β-D-glucosaminidase activity are used to evaluate possible renal effects of uranium in humans [K26, K28] or in animals [G27]. The use of osteopontin as a potential bioindicator of uranium effects was recently investigated in a combined experiment and human study [P30]. A decreased osteopontin level in urine was found when the concentration of uranium in urine, after acute exposure, exceeded 30 µg/L. Such a decrease may suggest renal damage induced by uranium exposure. However, no clear relationship between exposure level, duration of exposure and observed renal effect can be drawn from the available studies on humans. One experimental study performed on rats at 40 mg/L of uranium in drinking water failed to demonstrate variations in renal osteopontin mRNA level in the kidneys [R27].

232. Zamora et al. [Z6] studied the effects of chronic ingestion of uranium via drinking water on human populations. They found statistically significant subtle changes in two of the biological indicators measured, namely ratios of glucose and LDH to creatinine excreted (table 13) that did not translate to any observed health effects. In addition, LDH excretion decreased with higher exposure. The excretion of β−2 microglobulin increased but the increase was not statistically significant.

233. Some biochemical parameters were measured in the urine of Gulf War veterans [M20, M22, M23, M24, M25, S32]. Table 14 summarizes some of the results obtained. None of the levels measured were statistically significantly different from control values. Glucose concentrations were lower for the high-exposed veterans whereas the concentrations of β-2 microglobulin and retinol binding protein were higher. The results of the study indicated that there were a few subtle trends in changes of biochemical parameter levels of exposure.

234. The use of omic techniques (genomics, proteomics and metabolomics) to screen unknown biological or toxicological effects is expanding to develop new bioindicators. Omic methodology has recently been used to screen mRNA, proteins or metabolome involved in the response to uranium exposure in various cell lines or in animals [G21, M6, P27, P29, T4, T5]. A recent study has demonstrated the relevance of metabolomics in cases of uranium exposure [G21]. The aim of this study was to assess the biological changes in rats caused by ingestion of natural uranium in drinking water over 9 months and to identify potential biomarkers related to such contamination. LC-MS metabolomics identified urine as an appropriate biofluid for discriminating the experimental groups. Of the 1,376 features detected in urine, the most discriminant molecules were metabolites involved in tryptophan, nicotinate, and nicotinamide metabolic pathways, in particular N-methylnicotinamide. These results are in accordance with a previous study that showed the role of N-methylnicotinamide in rats with experimental renal failure induced by uranium [S12]. The study of Grison et al. thus establishes the validity of using metabolomics to address chronic low-dose uranium contamination [G21]. These studies show that while reliable biomarkers of tissue damage are not yet available, modern techniques have the potential to identify such molecules.

Table 13. Inter-subject variability in bioindicator data (adapted from [Z6])

Urinary parameter	*Low exposure[a] (<1 µg U/L (n=20))*	*High exposure[a] (2–781 µg/L (n=30))*
Mass of glucose excreted (mg/d)	55.9 (20.2–111)	82.4 (32.7–427)
Mass of LDH per unit mass of creatinine excreted (U/g)	25 (7.6–66)	17 (0–410)
Mass of β-2 microglobulin per unit mass of creatinine excreted (µg/g)	43 (11–270)	56 (15–340)

[a] Median value with range provided in brackets. The group 'Low exposure' is considered as the control group.

Table 14. Bioindicator data for Gulf War veterans (adapted from [M23])

Urinary parameter	*Normal range*	*Low exposure[a] (<0.1 µg uranium per gram of creatinine (n=25))*	*High exposure[a] (≥0.1µg uranium per gram of creatinine (n=10))*
Glucose g/day	0.0–0.5	6.3±4.38	0.12±0.01
β-2 microglobulin µg/g creatinine	0–160	59.08±7.48	81.72±13.28
Urine retinol binding protein µg/g creatinine	<610	31.00±4.73	48.11±9.73

[a] mean ± standard error.

VIII. EPIDEMIOLOGICAL STUDIES

235. Several population groups have been considered for epidemiological studies on the health effects of uranium due to occupational (uranium mines, milling and processing plants, facilities involved in the nuclear fuel cycle) or to environmental exposure (elevated uranium levels in drinking water, vicinity of uranium processing facilities or areas affected by depleted-uranium-munition use). Clear and comparative epidemiological information is limited. Nonetheless, in appendix A, tables A1–A4 summarize the principal studies and characterize their value in assessing uranium risks for occupational exposure, and tables A5 to A7 for environmental exposure.

A. Studies of occupational exposure

236. The preparation of the fuel used in nuclear power plants relies on a complex cycle, including the steps of mining, crushing of the ore and preparation of Yellowcake (uranium mills and processing plants), conversion of uranium oxide to UF_6, enrichment, and fuel manufacturing. Other activities include research and reprocessing of the nuclear fuel. These activities involve different types of jobs and different patterns of uranium exposure. Also, historical methods of individual exposure monitoring vary (measurement of ambient exposure, bioassay of excreted uranium, personal film dosimeters, in vivo measurements).

237. Studies of workers involved in the nuclear fuel cycle present a good potential to investigate cancer and other health effects of internal uranium exposure on the basis of long-term follow-ups, insofar as they have individual estimates of exposure levels. These studies have been identified as among the most pertinent ones to quantify a potential exposure-risk relationship [L16].

1. Uranium miners

238. Miners are exposed to internal contamination due to inhalation of long-lived radionuclides (LLR) from uranium ore dust, but also to external gamma radiation and radon and its progeny. The main source of radiological exposure of uranium miners is radon and its decay products. Many epidemiological studies of uranium miners have been performed that demonstrated an association of accumulated exposure to radon and its decay products with lung cancer risk [I16, L17, N1, U9, W17].

239. A concerted European effort (Alpha risk project) [T10] has furthered the assessment of health risks associated with uranium exposure based on the Czech, French CEA-COGEMA and German Wismut cohorts. Individual exposure to uranium was estimated from measurement of ambient concentration (in Bq/m^3). The assessment of uranium contamination in miners was based on the reconstruction of individual accumulated ore dust exposure over time. The development of dedicated dosimetric software enabled the estimation of cumulative organ doses due to radon and its progeny, LLR arising from uranium ore dust, and external gamma ray exposure [M10, M11]. This approach allowed the estimation of the contribution of uranium exposure to the total organ dose, and the initiative has resulted in a number of cohort and nested case-control studies of uranium exposure and mortality by cancers, leukaemia or cardiovascular diseases [D23, D31, K15, K17, M50, M51, M52, R4, R5, T13, V2]. A difficulty with the uranium miner studies is that the lung doses from short-lived radon decay products are much larger than and often correlated with the LLR exposure from uranium, which hampers the assessment of exposure effects for lung cancer.

2. Uranium millers

240. The first steps after uranium extraction are crushing of the ore and preparation of the Yellowcake by uranium millers or as part of uranium processing. Like the miners, millers are subjected to inhalation of radon and radon decay products, external gamma radiation and inhalation of LLR from uranium ore dust. One potential constraint of uranium miller studies is that, despite uranium LLR exposure being a higher percentage of total radiation dose, uranium miller exposure is typically much lower than uranium miner total exposure. Individual exposure to uranium among millers has been estimated solely from measurement of ambient concentration (in Bq/m^3).

241. Only a few cohort studies have specifically considered health risks among uranium millers [B36, K17, P21, Z1]. These studies reported mortality results, but only the German miller study estimated individual LLR exposure from uranium ore dust and potential health risk [K18]. They studied 4,054 millers who had never worked in underground or open pit mines and assessed mortality from various diseases in relation to their exposure to radon, external gamma ray, LLR and silica dust exposure [K18].

3. Nuclear fuel cycle workers

242. A variety of epidemiological studies enabled the estimation of health risks among workers involved in the fuel nuclear cycle: in the United States (Fernald; Rocketdyne; Oak Ridge TEC, Y-12 and K-25; Paducah; Linde; Mallinckrodt), in the United Kingdom (UKAEA and AWE composite cohorts, Sellafield), and in France (CEA; AREVA NC; Eurodif) [C5, Z9, Z10].

243. After milling, the nuclear fuel cycle entails different successive steps, including conversion, enrichment, fuel manufacturing, reprocessing and research. These steps involve diverse radiological and chemical exposure to different forms of uranium compounds. However, as these steps are not distinguished in most of the epidemiological studies, they are considered together in this section. Individual exposure to uranium has often been estimated solely from measurement of ambient concentrations. Uranium exposure is preferably estimated from bioassays of individuals' excreted uranium or by other personal measurement (in vivo counting). In most studies exposure estimates for workers could be based only on ambient measurements at job locations or even extrapolations for time and location with no available ambient measurements.

4. Results of occupational exposure studies

244. The exposure situations may influence cancer risk in occupational settings, especially for lung cancers. For miners, the main exposures are from radon (internal exposure), external gamma radiation, and exposure to uranium dust. Typically, workers in the nuclear fuel production are subjected to less radon exposure but additional potentially toxic chemical exposure. In addition, for lung cancer, confounding factors may occur due to variations in smoking habits, about which most studies contain little or no information. Exposure levels have been assessed differently in various studies depending on the occupational exposure setting and the historical exposure information available.

245. Characteristics and results of uranium miner, miller and processor studies are summarized in appendix A, tables A1–A4, with the studies in tables A3 and A4 having more quantitative analyses. The health outcomes are described below by organ systems. Since well-conducted nested case-control studies provide risk estimates that in principle are comparable to those from the full cohort, the results of both types of studies are provided together without distinction.

246. Studies that have identified uranium-exposed cohorts have varied in the amount of data they presented to adduce uranium health effects. Studies that contain a subset of uranium-exposed workers who are not actually identified as exposed provide essentially no information on uranium effects; most studies in appendix A, table A1 fall into this category. Others have identified uranium workers but have no individual exposure levels and therefore provide only standardized mortality ratios (SMRs) or other overall statistics which yield little valid information on uranium effects because they consider those with appreciable exposure and little or no exposure as a composite group. Also, SMRs are subject to "healthy worker bias"; such studies are shown mainly in appendix A, table A2. Analyses by duration of employment can also be subject to "healthy worker survivor bias" and therefore should be viewed circumspectly. Analyses that show SMRs or relative risks (RRs), including hazard ratios (HRs) and odds ratios (ORs) by cumulative dose groups are somewhat informative, but difficult to interpret since the common problem of small numbers within groups leads to inconsistencies in risk estimates across groups; trend analysis summaries are helpful but fail to provide quantitative overall risk estimates (appendix A, table A3). Studies that provide quantitative risk estimates per unit of exposure are presented in appendix A, table A4.

247. Studies that explicitly estimate individual uranium exposure and use those data to calculate quantitative dose-response associations with specific health end points are valuable for assessing risk. Typically, dosimetric estimates are made for detailed types of jobs at particular work locations for specific periods based on ambient monitoring data, and this job exposure matrix (JEM) is applied to individual work records. Better individual dosimetry is achieved when individual urinalyses of uranium excretion or other personalized measurements are available, supplemented by ambient monitoring. However, some quantitative studies had limited ability to distinguish effects from LLR exposure from uranium from those associated with external irradiation or radon decay products because those doses were much larger than the LLR doses to organs. That problem applies especially to lung cancer among miners, since radon decay products usually contribute much more lung dose than LLR, so that in miner studies the LLR lung dose was often only 1–2% as great as the radon decay product dose and the two doses are typically correlated. In that situation, estimates of LLR-associated risk may be inaccurate to an unknown degree.

248. The following overview of associations of LLR exposure from uranium with diseases thought to be induced by uranium will concentrate on the most informative studies that have presented quantitative dose-response data. The most recent reports of study cohorts are shown in preference to older reports to avoid redundancy of information, since the most recent data with longer follow-up and sometimes improved dose information provide better risk estimates.

249. The study results will be considered by organ systems. Essentially, all the informative studies of occupational populations exposed to uranium have been conducted since 1980, some with exposure dating back to the mid-1940s. These studies considered a large range of potential health effects. Among the most frequently considered ones are respiratory cancers (lung, laryngeal), urological cancers (kidney, bladder, prostate), digestive cancers (stomach, intestine, liver, pancreas), cancers of brain and central nervous system, lympho-haematopoietic malignancies (leukaemia, lymphoma, multiple myeloma). Non-cancer diseases have also been considered, especially respiratory, circulatory and renal system diseases. Further details about these studies are presented in appendix A, table A4.

(a) *Lung cancer and other respiratory diseases*

250. *Lung cancer.* Studies with quantitative risk estimates for respiratory diseases from LLR exposure from uranium are presented in table 15. Ten reports were found that had dose-response estimates for lung cancer risk based on individualized estimates of uranium exposure. The study of CEA-COGEMA miners in France reported a positive risk coefficient for LLR exposure from uranium, though the radon and external-radiation co-exposure make the result difficult to interpret. Other miner studies have not characterized and analysed LLR exposure from uranium and lung cancer. The German study of uranium millers [K18] reported a dose-response analysis of LRR exposure from uranium and lung cancer risk. The association was non-significant and in the negative direction. Two other studies of uranium millers reported no significant elevation in lung cancer mortality [B36, P21].

251. The remaining eight reports of LLR dose-related lung cancer mortality were based on workers in nuclear processing industries. The nature of the workplaces and the types of measurements and procedures that generated the individual exposure estimates are given in appendix A, table A4, for the various studies. The large study of Fernald workers, with 269 lung cancer deaths, showed a positive, but non-significant, association and most other studies had negative or non-significant coefficients of risk. Additional uranium worker cohorts showed no significant elevation in overall lung cancer SMRs [C36, D33, D34, M26, M27]. However, the relatively small French study of the AREVA NC Pierrelatte plant showed significant positive dose responses [G31]. This is the only study that conducted separate analyses for exposure to uranium compounds that differ in solubility (Types: F, M and S). They found

the Type M and Type S exposure conferred lung cancer risk (table 15). In a further analysis [G32] that distinguished exposure to natural uranium from the reprocessed uranium which has a different isotope composition, they found that risks were especially dose related for reprocessed uranium of the Type M and Type S. This suggests that insoluble uranium particles with a longer residence time in the lung confer more risk than the more soluble particles with a shorter residence time. However, these interesting results were based less than 55 lung cancer deaths and require confirmation in larger studies.

Table 15. Dose-response studies of uranium exposure and risk of respiratory system diseases

Study references	*No. of deaths*	*Nature of uranium work*	*Unit of uranium (LLR) exposure*	*Risk estimate per unit LLR exposure*[a]
LUNG CANCER				
France, CEA-COGEMA [R5] (Also [R4, V2])	94	Mining	kBqh/m^3	ERR=0.32 (95% CI: 0.09, 0.73)
Germany, milling [K18]	159	Milling	100 kBqh/m^3	ERR=−0.61 (95% CI: −1.42, 1.9)
France, AREVA NC [C6]	48	Processing	Years of Types F, M, and S uranium exposure	HR=1.01 (95% CI: 0.96, 1.01) [F] 1.07 (1.01, 1.13) [M] 1.07 (1.01, 1.14) [S]
France, AREVA NC [G32]	53	Processing	Years of exposure to Types F, M and S reprocessed uranium	HR=1.07 (95% CI: 0.96, 1.19) [F] 1.13 (1.03, 1.25) [M] 1.13 (1.01, 1.25) [S]
USA, TEC/Y-12/ Mallinckrodt/ Fernald [D35][b]	787	Processing	0.5, 2.5, 5, 25, 50, ≥250 mGy LLR	OR=1.03, 0.57, 0.85, 0.82, 0.64, 2.05 (95% CI: 0.20, 21), respectively[c]
USA, Rocketdyne [B38]	94	Processing	100 mSv LLR	RR=1.01 (95% CI: 0.89, 1.16)
USA, Fernald [S19]	269	Processing	mGy LLR	ERR=0.022 (95% CI: −0.009, 0.06)
USA, Paducah gaseous diffusion [C17]	129	Processing	µg.y	RR=0.91 (95% CI: 0.5, 1.6) (21–50 µg.y) 0.95 (0.6, 1.6) (51–125 µg.y) 0.51 (0.3, 0.9) (>125 µg.y)
USA, Y-12 [R12]	111	Processing	10 mSv LLR	ERR=−0.77 (95% CI: −2.5, 1.0)
France, Gaseous diffusion [Z10]	100	Processing	Low, medium, high	Exposure to natural soluble uranium compounds (with 90% CI): Medium: RR=0.92 (CI: 0.54, 1.6) High: RR=0.74 (CI: 0.42, 1.3) Enriched uranium (n=23): Medium RR=1.8 (CI: 0.64, 4.6) High RR=0.69 (CI: 0.21, 1.9) Depleted uranium (n=23): Medium RR=1.2 (CI: 0.33, 3.7) High RR=1.5 (CI: 0.61, 3.9)
EXTRATHORACIC RESPIRATORY CANCERS				
Germany, Wismut [M51]	554	Miners	10 kBqh/m^3	ERR=0.098 (95% CI: −0.11, 0.31) (Laryngeal cancer)
Germany, Wismut [K17]	234	Miners	100 kBqh/m^3	ERR=−0.17 (95% CI: −2.50, 2.16) (All extra-thoracic airway cancers)

Study references	*No. of deaths*	*Nature of uranium work*	*Unit of uranium (LLR) exposure*	*Risk estimate per unit LLR exposure*[a]
NON-MALIGNANT RESPIRATORY DISEASE				
France, CEA-COGEMA [R5]	37	Miners	kBqh/m^3	ERR=−0.086 (95% CI: n.e.)[d]
USA, Y-12 [R12]	50	Processing	100 mSv	ERR=−0.085 (90% CI: −0.32, 0.15)
USA, Fernald [S19][e]	102	Processing	100 µGy LLR	ERR=−0.0062 (95% CI: −0.007, 0.0006)

[a] Risk estimation metrics: ERR (excess relative risk) for which zero represents no excess or deficit; HR (hazard ratio) and RR (relative risk or rate ratio) are expressed as a multiple of the rate in the baseline (lowest/no exposure) group. (ERR = RR – 1).

[b] This study [D35] was partially repeated later on [R12, S19] but included two cohorts that were not reported elsewhere.

[c] The risk estimate of 2.05 for the ≥250 mGy group became 0.36 in an analysis with adjustment for smoking.

[d] Not estimable from the likelihood profile.

[e] Analysis of chronic obstructive pulmonary disease.

252. In summary, there is mixed evidence for the lung carcinogenicity of uranium. The inconsistency may relate to variations in the amount and types of exposure data available (e.g. extrapolated dose reconstruction, ambient monitoring, uranium urinalyses or other personalized exposure measures) or to variations in methods for calculating LLR doses from the raw data. The inconsistency can also relate to other radiation or chemical exposure that may not have been adequately accounted for in the LLR analyses, or to dose-dependent variations in smoking behaviours. On the other hand, since the studies have low statistical power to detect risks, given the relatively small numbers of lung cancers and fairly low levels of LLR exposure from uranium for most workers, it is notable that two cohorts with dose-response data showed a statistically significant association [C6, R5].

253. *Other respiratory cancers.* A study of all extrathoracic airway cancers, based on a well-defined cohort of the German uranium miners, showed a negative dose-response coefficient for LLR exposure from uranium [K17]. Another study of German uranium miners had LLR dose-response data for laryngeal cancer, which yielded a non-significantly positive risk coefficient [M51]. There was no association of LLR exposure from uranium and laryngeal cancer among French uranium miners [R5]. Other studies have reported overall excess laryngeal or upper airway cancers in worker populations potentially exposed to uranium [B18, B29, B33, D35, G31], but those are based on small numbers of cancers, without individual uranium exposure estimates, and with limited information on the risk factors of smoking and alcohol intake.

254. *Non-malignant respiratory disease (NMRD).* Four studies with dose-response analyses all reported negative dose-response coefficients for NMRD [B38, R5, R12, S19]. Pinkerton et al. [P21] reported an inverse relationship of NMRD with length of time working in uranium milling. SMRs in a number of other cohorts with uranium exposure were not significantly elevated [C20, C36, D33, D34, M26, M27, R14, Z10] so there is no evidence that NMRD is associated with uranium exposure.

(b) *Lymphatic and haematopoietic cancer*

255. *Leukaemia.* Since leukaemia shows a large excess relative risk from radiation exposure, it is a strong a priori candidate to investigate regarding uranium exposure effects. Table 16 shows uranium dose-response related results for leukaemia. A nested case-control study of leukaemia mortality within the large collection of German Wismut miners [M50] found a positive but non-significant association of estimated LLR exposure with non-chronic lymphocytic leukaemia (non-CLL) risk. The positive risk coefficient was driven entirely by the highest dose group (≥20 kBqh/m^3, ERR=1.26, 90% CI: 0.7, 2.2,

n=14). A smaller miner study in Czechia found a statistically significant dose-response association of leukaemia mortality with total red bone marrow dose, of which the majority was from LLR exposure [T13]. Three smaller dose-response studies of leukaemia risk in the uranium processing industries did not support excess risk (table 16). In summary, there is limited dose-response evidence for an association of uranium exposure with subsequent leukaemia. Atkinson et al. [A29] reported a non-significant SMR (SMR=1.10; 95% CI: 0.89, 1.33; n=103) in nuclear workers, particularly among workers monitored for internal radiation exposure. Others likewise have reported non-significant overall SMRs in uranium worker cohorts [C36, D30, D33, D34, L44, M26, M27, P24, S5, Z2, Z10], but did not estimate worker uranium doses or conduct LLR dose-related analyses.

256. *Other lympho-haematopoietic malignancies.* Lymphoma is a biologically plausible outcome of inhalation exposure to uranium, since uranium deposited in the lung tends to migrate to the thoracic lymph nodes. However, there are few studies providing dose-dependent analyses of uranium exposure and lympho-haematopoietic malignancies other than leukaemia (table 16). The cohort of German uranium millers [K18] showed a non-significant negative risk coefficient for all lympho-haematopoietic malignancies. In the Rocketdyne cohort there was a non-significant positive dose-response [B38], though the specifics were not reported. A French study of gaseous diffusion plant workers reported a non-significant excess risk for all lympho-haematopoietic malignancies other than leukaemia among those with medium or high exposure to soluble uranium [Z10]. A study in the United States showed for uranium miners an elevated risk of lympho-haematopoietic malignancies (SMR=1.38, 95% CI: 1.03, 1.82) [S5]. Pinkerton et al [P21] showed a suggestive excess of lymphatic and haematopoietic malignancies, excluding leukaemia, (SMR=1.44, 95% CI: 0.83, 2.35, n=16) with no dose response.

257. A study of non-Hodgkin's lymphoma (NHL) at the Paducah gaseous diffusion plant [C17] produced high relative risks, but the fact that there was no dose response suggests that the high values are likely attributable to a deficit of NHL in the baseline comparison group rather than large excesses in the other dose groups. NHL mortality was non-significantly elevated for exposure to uranium in the Fernald cohort [S19]. The Czech uranium miner study [T13] indicated a non-significantly elevated SMR of 1.4 (95% CI: 0.9, 5.1, n=16) for NHL but did not provide a dose-response analysis. Other uranium worker cohorts reported null overall SMRs for lymphomas or all lympho-haematopoietic cancers [B38, C9, C36, D30, D33, D34, G31, L44, M27, P21, P24, S5, Z2].

258. In the study at the Oak Ridge K-25 gaseous diffusion plant by Yiin et al. [Y3] with a dose-response analysis of multiple myeloma and uranium exposure, a significant association was not found. A significant overall excess of multiple myeloma was found among United States miners (SMR=1.97, 95% CI: 1.05, 3.37, n=13), and an excess based on two cases (SMR=8.38; 90% CI: 1.44, 26.20) was reported among French CEA-COGEMA uranium processing workers [B9]. A non-significant excess of multiple myeloma was observed among Mallinckrodt uranium processing workers [D33] (SMR=1.30, 95% CI: 0.42, 3.0, n=5). The SMRs for multiple myeloma were not significantly elevated in other uranium worker groups [C17, Z2].

Table 16. Dose-response studies of uranium exposure and risk of lympho-haematopoietic malignancy mortality

Study references	*No. of deaths*	*Nature of uranium work*	*Unit of uranium (LLR) exposure*	*Risk estimate per unit LLR exposure* [a]
LEUKAEMIA				
Germany, Wismut [M50]	218 (non-CLL)[b]	Mining	100 kBqh/m^3	ERR=0.76 (90% CI: −1.26, 2.78)
Czechia [T13]	30	Mining	Sv[c]	ERR=2.5 (90% CI: 0.3, 9.3)
USA, Paducah [C17]	21 (all types)	Processing	#1 (0–20 µg.y) #2 (21–50 µg.y) #3 (51–125 µg.y) #4 (>125 µg.y)	Baseline #2: RR=0.73 (95% CI: 0.2, 3.0) #3: RR=0.49 (CI: 0.2, 2.3) #4: RR=0.77 (CI: 0.2, 2.5)
USA, Rocketdyne [B38]	10 (non-CLL)	Processing	100 mSv LLR	RR=1.06 (95% CI: 0.50, 2.23)
USA, Fernald [S19]	28 (non-CLL)	Processing	100 µGy LLR	HR=0.18 (95% CI: 0.012, 0.80)
OTHER LYMPHO-HAEMATOPOIETIC MALIGNANCIES				
Germany [K18]	23 (all lympho-haematopoietic)	Millers	100 kBqh/m^3	ERR= −0.65 (95% CI: −2.78, 1.47)
Zhivin, Gaseous diffusion [Z10]	28 (all lympho-haematopoietic)	Processing	Medium and high exposure	Natural soluble uranium compounds (with 90% CI): Medium RR=1.4 (CI: 0.52, 3.9) High RR=1.08 (CI: 0.37, 3.3)
USA, Paducah [C17]	26 (non-Hodgkin's lymphoma)	Processing	#1 (0–20 µg.y) #2 (21–50 µg.y) #3 (51–125 µg.y) #4 (>125 µg.y)	Baseline #2: RR=9.95 (95% CI: 1.2, 81) #3: RR=8.85 (CI: 1.1, 71) #4: RR=5.74 (CI: 0.7, 45)
USA, Fernald [S19]	12 (non-Hodgkin's lymphoma)	Processing	100 µGy	HR=1.2 (95% CI: 0.88, 1.5)
USA, K-25 [Y3]	98 (multiple myeloma)	Processing	10 µSv	OR, 1.04 (95% CI: 1.00, 1.09)

[a] Risk estimation metrics: ERR (excess relative risk) for which zero represents no excess or deficit; HR (hazard ratio) and RR (relative risk or rate ratio) are expressed as a multiple of the rate in the baseline (lowest/no exposure) group. (ERR = RR – 1).

[b] Non-CLL, all leukaemias except chronic lymphocytic leukaemia.

[c] Analysis was for total red bone marrow dose, of which 52–64% was estimated to be due to LLR from uranium dust inhalation.

(c) *Digestive system cancer*

259. *Stomach cancer*. Only a few studies have conducted dose-dependent analyses of uranium exposure and digestive system cancers (table 17). Studies of German uranium millers [K18], the Fernald uranium processors [S19], and Rocketdyne workers with internal exposure monitoring [B38] all showed weakly positive but non-significant dose-response risk estimates for stomach cancer. The risk of mortality from stomach cancer was increased with the alpha absorbed stomach dose among German uranium miners (ERR per Gy=37.3; 95% CI: 3.4, 71.1, n=592), but the contribution of LLR to

the absorbed stomach dose was less than 1% [K15]. Other uranium worker cohorts reported null overall SMRs for stomach cancer [B38, C9, C17, D34, L44, M26, R5, S5, Z1, Z10].

260. *Intestinal cancer.* The study of German uranium millers showed non-significant ERR coefficients for both colon and rectal cancers [K18], and both the French uranium miners study [R5] and the Rocketdyne study [B38] reported non-significant LRR dose coefficients for colorectal cancers. On the other hand, a dose-response analysis of combined small intestine and colon (but not rectum) cancer at the United States Fernald uranium processing plant yielded a statistically significant excess risk [S19]. Since this result was based on relatively small numbers, it is in need of confirmation by larger studies. Other uranium worker cohorts reported null overall SMRs for colon or colorectal cancers [C9, D33, D34, G31, L44, M26, P21, Z1, Z10] but did not conduct LLR dose-related analyses.

261. *Pancreatic cancer.* The United States Paducah [C17] and Fernald [S19] studies provided dose-response analyses of pancreatic cancer after LLR exposure (table 17). Neither study provided an indication of an association with uranium exposure, nor did the studies of French uranium miners [R5] or Rocketdyne workers [B38]. However, the studies had relatively small numbers of pancreatic cancers and thus limited statistical power. Other reports have indicated non-significant SMRs for pancreatic cancer in uranium processing workers [C36, D33, D35, L44, M26, Z1, Z10] but did not estimate worker uranium doses or conduct LLR dose-related analyses.

Table 17. Dose-response studies of uranium exposure and risk of digestive system disease mortality

Study references	*No. of deaths*	*Nature of uranium work*	*Unit of uranium (LLR) exposure*	*Risk estimate per unit LLR exposure* [a]
STOMACH CANCER				
Germany, [K18]	49	Milling	100 kBqh/m^3	ERR=1.5 (95% CI: −2.9, 5.9)[b]
USA, Fernald [S19]	29	Processing	100 µGy	ERR=0.041 (95% CI: −0.20, 5.6)
INTESTINAL CANCER				
Germany, [K18]	22 (colon)	Milling	100 kBqh/m^3	ERR=–0.07 (95% CI: –3.3, 3.2)
Germany, [K18]	26 (rectum)	Milling	100 kBqh/m^3	ERR=0.56 (95% CI: –3.1, 4.2)
USA, Fernald [S19]	48 (colon & small intestine)	Processing	100 µGy	ERR=1.5 (95% CI: 0.12, 4.1)
PANCREATIC CANCER				
USA, Paducah [C17]	30	Processing	#1 (0–20 µg.y) #2 (21–50 µg.y) #3 (51–125 µg.y) #4 (>125 µg.y)	Baseline #2: RR=1.42 (95% CI: 0.4, 4.7) #3: RR=0.49 (95% CI: 0.1, 1.9) #4: RR=0.97 (95% CI: 0.3, 3.0)
USA, Fernald [S19]	41	Processing	100 µGy	HR= 0.61 (95% CI: 0.015, 3.5)

[a] Risk estimation metrics: ERR (excess relative risk) for which zero represents no excess or deficit; HR (hazard ratio), RR (relative risk or rate ratio) and OR (odds ratio for case-control studies) are expressed as a multiple of the rate in the baseline (lowest/no exposure) group. (ERR = RR – 1).

[b] Estimate is adjusted for radon exposure levels.

262. *Liver cancer.* Dufey et al. [D31] observed a non-significant increase in liver cancer mortality risk associated with high-LET absorbed liver dose among German uranium miners (ERR per Gy=48.3; 95% CI: −32.0, 128.6 (n=159) after adjustment for low-LET dose). However, the contribution of LLR to the absorbed liver dose was less than 2%, so the association is not informative regarding uranium risk. Among French uranium miners there was also a non-significant association of LLR exposure and liver

cancer risk [R5]. Other uranium worker cohorts reported non-significant SMRs for liver cancer [B38, C9, M26, M27, P24, R5, Z10] but had no uranium dose-response analyses.

263. In summary, there is no persuasive evidence of an association between uranium exposure and digestive cancers. The effect, if any, is likely small. However, the relatively small numbers of digestive cancer cases and consequent limited statistical power to detect effects make any conclusion uncertain.

(d) *Kidney and other urological cancers*

264. *Kidney cancer.* The toxicological data suggest that uranium exposure may be related to urological cancers, especially to the kidney because of the potential for both adverse radiological and metal effects upon that organ. The available epidemiological studies with dose-response results are shown in table 18. Dose-response analyses of kidney cancer in relation to LLR exposure have been conducted for the cohorts of miners in France and Germany [D23]. Neither cohort showed a significant association with kidney cancer even though the large German miner cohort had a substantial number of renal cancers. In the French CEA-COGEMA cohort, the overall SMR was elevated for kidney cancer (SMR=2.0, 95% CI: 1.2, 3.1, n=20), but LLR analyses were not reported [V1].

Table 18. Dose-response studies of uranium exposure and risk of urological system disease mortality

Study references	*No. of deaths*	*Nature of uranium work*	*Unit of uranium (LLR) exposure*	*Risk estimate per unit LLR exposure* [a]
KIDNEY CANCER				
France, CEA-COGEMA [D23]	11	Mining	kBqh/m^3	HR=0.89 (95% CI: 0.55, 1.42)
Germany, Wismut [D23]	174	Mining	kBqh/m^3	HR=1.009 (95% CI: 0.991, 1.027)
Germany [K18]	11	Milling	100 kBqh/m^3	ERR=7.36 (95% CI: –11, 26)
USA, Fernald [S19]	15	Processing	100 µGy	ERR=0.039 (95% CI: –0.021, 0.55)
OTHER UROLOGICAL DISEASES				
Germany [K18]	30 (Prostate cancer)	Milling	100 kBqh/m^3	ERR=0.21 (95% CI: –2.8, 2.4)
USA, Fernald [S19]	19 (chronic kidney disease)	Processing	100 µGy	HR=0.98 (95% CI: 0.78, 1.1)

[a] Risk estimation metrics: ERR (excess relative risk) for which zero represents no excess or deficit; HR (hazard ratio) and RR (relative risk or rate ratio) are expressed as a multiple of the rate in the baseline (lowest/no exposure) group. (ERR = RR – 1).

265. The study of German uranium millers [K18] had a large risk coefficient for kidney cancer but the association was non-significant because the number of cases was small (n=11) and consequently the confidence interval of the estimate was very wide. The dose-response coefficients for the Fernald uranium processing workers [S19], the Rocketdyne workers [B38] and the French uranium miners [R5] were all non-significant. Overall SMRs for kidney cancer were found to be increased in two uranium-processing facilities: Y-12 [C20, L44] and Capenhurst [M26]. But at Capenhurst, the increase was limited to unexposed workers. The UK Nuclear research workers also experienced elevated mortality from kidney cancer [B18, C8]. However, none of these studies included an investigation of the relation with internal exposure to uranium. Other uranium worker studies did not report significantly elevated overall SMRs for kidney cancer [C9, C17, L44, S5, Z10] but had no uranium dose-response analyses.

266. *Bladder cancer.* French uranium miner studies reported a non-significant LLR dose-response association with bladder cancer [R5]. An increase in mortality (an elevated overall SMR) from bladder cancer was reported among Fernald workers [D35]. It was potentially associated with a high exposure to the cutting fluids used during uranium metal production but not with internal exposure to uranium compounds [R14]. In a more recent study of the Fernald workers [S19], elevated mortality was observed only among salaried female workers; for cancer of the bladder and other urinary organs, the SMR was 5.13 (95% CI: 1.06, 15.0; n=3). However, the small number of cases, no increase in bladder cancer mortality among males (n=21) or hourly paid female workers (n=0), and no dose-response information argue against a meaningful excess [S19]. Other reports have indicated non-significant risks (usually SMRs) for bladder cancer in uranium processing workers [B38, Z1, Z10], but did not estimate worker uranium doses or conduct LLR dose-related analyses.

267. *Prostate cancer.* The recent study of German uranium millers analysed uranium dose and prostate cancer risk and found no evidence of an association [K18], albeit the number of prostate cancer deaths was small (table 18). The study of United States Rocketdyne workers reported a non-significant dose-response trend in the negative direction for prostate cancer (n=63), but did not provide a risk coefficient [B38]. The LLR dose-response trend among French uranium miners was likewise non-significant [R5].

268. Radiation-exposed worker cohorts with excess prostate cancer have been investigated for internal radionuclide exposure in the UK Atomic Energy Authority cohorts [A28, B18, R22] but with only a limited examination of uranium exposure. Rooney et al. [R22] conducted a nested case-control examination of the relation between prostate cancer and occupational exposure in those cohorts, including 136 prostate cancer cases and 404 controls and examination of 29 radionuclides. Three cases and twelve controls had an indication of potential uranium exposure, and zero cases and six controls had documented uranium exposure (RR=0, 95% CI: 0, 2.55), so no effect on prostate cancer mortality was observed. Other studies have reported non-significant overall SMRs for prostate cancer among uranium workers [D33, L44, M26, Z1, Z10] but had no uranium dose-response analyses.

269. In summary, except for the German Wismut cohort, the number of kidney cancers was very small, thus constraining the ability to detect small-to-moderate effects. Since the studies of kidney cancer and chronic kidney disease are uniformly negative, the risk of uranium exposure for kidney cancer is weak or absent. The data do not generally support an increase in bladder cancer associated with uranium exposure; in fact, the only dose-response report regarding bladder cancer risk had a negative coefficient [B38]. The two studies that have evaluated dose-response data for prostate cancer did not show a significant association.

(e) *Brain and central nervous system cancers*

270. Experimental evidence indicates that uranium compounds, particularly more soluble ones, cross the blood-brain barrier, thereby potentially putting the brain at risk. There have been only a small number of studies with dose-response analyses of brain and central nervous system (brain/CNS) tumours (table 19). An analysis of brain/CNS tumours by LLR dose groups was conducted among Paducah gaseous diffusion uranium enrichment workers [C17], but no trend by dose was seen. A study of French uranium miners reported a non-significantly positive brain/CNS tumour dose-response risk for LLR exposure, accompanied by an overall excess (SMR=1.71, 95% CI: 1.00, 2.74) [R5]. Similarly, three United States studies of uranium processing workers did not find a dose-related excess of brain/CNS tumours [B38, C17, C20].

271. Carpenter et al. [C7] investigated the possible association between brain/CNS cancers and exposure to external and internal radiation among Oak Ridge Y-12 workers. The internal dose to the

lung, calculated as in the study by Checkoway et al. [C20], was used as a surrogate for the internal dose to the brain for the 47 cases and 120 matched controls. Odds ratios (ORs) were non-significantly elevated for categories of cumulative lung dose: ≥150 to 290 mSv (OR=2.8; 95% CI: 0.7, 11.9; n=5); ≥300 to 450 mSv (OR=2.7; 95% CI: 0.8, 9.3; n=5); and among workers with mean annual lung dose >150 mSv (OR=1.7; 95% CI: 0.7, 4.2; n=16). No dose–response trend was observed after adjustment for possible confounding factors (26 different chemicals, socio-economic status, duration of employment), using either a 5- or 10-year dose lag. Other studies of uranium worker cohorts indicated no significant overall excess of brain/CNS tumour deaths [C9, D33, L44, M26, M27, P24, R14, Z10] but did not estimate worker uranium doses or conduct LLR dose-related analyses.

272. A limiting factor in all of these studies was the very small numbers of tumours, so only quite a large excess risk would be detectable. Clearly more data are needed to make a better judgment about brain/CNS tumour risk from uranium exposure.

Table 19. Dose-response studies of uranium exposure and risk of brain and central nervous system (CNS) tumour mortality

Study references	*No. of deaths*	*Nature of uranium work*	*Unit of uranium (LLR) exposure*	*Risk estimate per unit LLR exposure* [a]
BRAIN/CNS TUMOURS				
France, CEA-COGEMA [R5] [Also [V2]]	17	Mining	kBqh/m^3	ERR=0.28 (95% CI: n.e. <0, 1.87)[b]
USA, Paducah [C17]	14	Processing	#1 (0–20 µg.y) #2 (21–50 µg.y) #3 (51–125 µg.y) #4 (>125 µg.y)	Baseline #2: RR=0.66 (95% CI: 0.1, 4.2) #3: RR=1.07 (95% CI: 0.2, 4.8) #4: RR=0.45 (95% CI: 0.1, 2.2)
USA, Y-12 [C20]	14	Processing	#1 (0–9 mSv) #2 (10–49 mSv) #3 (≥50 mSv LLR)	Baseline #2: RR=1.10 (95% CI: 0.2, 6.5) #3: RR=0.45 (95% CI: 0.1, 3.2)

[a] Risk estimation metrics: ERR (excess relative risk) for which zero represents no excess or deficit; HR (hazard ratio) and RR (relative risk or rate ratio) are expressed as a multiple of the rate in the baseline (lowest/no exposure) group. (ERR = RR – 1).

[b] n.e. = not estimable from the likelihood profile.

(f) *Circulatory diseases*

273. Suggestive findings from external radiation studies over the past 15–20 years have prompted examinations of circulatory disease risks as a potential radiation effect of internal radionuclides. The available studies of uranium exposure have evaluated the risk for all circulatory system diseases (CSD) and major subcategories of CSD, namely ischaemic heart diseases (IHD) and cerebrovascular diseases (CeVD) (table 20).

274. *Circulatory system diseases*. The German Wismut miner cohort is the largest to study uranium associated CSD risk. They reported a negative CSD risk coefficient for internal LLR exposure on the basis of 5,417 CSD deaths [K14]. Two reports of CSD in the French CEA-COGEMA miner cohort are of interest (table 20). A report of the entire cohort indicated a non-significantly positive risk coefficient [R5], while another report of the subset of the cohort for whom information on radon, external radiation exposure, and medical risk factors for CSD also was available showed a nearly significant risk of CSD from LLR exposure after accounting for the other factors [D24].

275. A report of the French AREVA NC uranium processing cohort found that exposure to Type M and Type S (less soluble) reprocessed uranium conferred statistically significant risk of CSD, as did Type S natural uranium exposure [G33], but Type F exposure did not. The study found statistically significant associations of CSD with the number of years exposed to Type S exposure to both reprocessed and natural uranium, and a near-significant association for Type M reprocessed uranium (table 20) [G33]. Less quantitative but supportive findings were that CSD mortality was increased overall among workers exposed to slowly soluble reprocessed (HR=2.13; 95% CI: 0.96, 4.70) and natural uranium (HR=1.73; 95% CI: 1.11, 2.69). In the subgroup of smokers, the risk estimates were higher but with larger CIs (HR=1.91; 95% CI: 0.92, 3.98 for natural uranium and HR=4.78; 95% CI: 1.38, 16.50 for reprocessed uranium). The AREVA NC findings suggested that types of uranium with a long residence time in tissues may confer risk of CSD.

276. McGeoghegan et al. [M29] reported an association between mortality from CSD and radiation exposure in males performing industrial work in the British Nuclear Fuels Limited cohort (BNFL). This cohort consisted partially of uranium workers (37% of the cohort were workers employed at the Springfields uranium processing plant and 6.7% at the Capenhurst uranium enrichment plant). Their analysis of internal exposure to any radionuclide gave a dose-response ERR per Gy of 0.76 (90% CI: 0.37, 1.23; n=2,275), but a dose-response analysis was not available specifically for uranium exposure.

277. *Ischaemic heart diseases.* The large German Wismut study of uranium miners found a negative risk coefficient for LLR exposure and the end point of all heart disease (table 20) [K14]. The other studies evaluated IHD as a cardiovascular end point. Studies of French uranium miners (CEA-COGEMA) reported negative risk coefficients for IHD for the entire cohort [R5] and for the subset where they could account for radon, external radiation, and medical heart disease risk factors [D24]. The German uranium miller study also reported a non-significantly negative risk coefficient for LLR dose [K18]. McGeoghegan et al. [M29] reported an association between mortality from IHD and radiation exposure in males performing industrial work at BNFL. Their analysis of internal exposure to any radionuclide gave a dose-response ERR per Gy of 0.52 (90% CI: 0.09, 1.06; n=1,494), but uranium exposure was not analysed.

278. *Cerebrovascular diseases.* The same set of studies also provided risk estimates for CeVD (table 20). The large German Wismut study of uranium miners found a negative risk coefficient for LLR exposure and CeVD [K14]. Studies of French uranium miners (CEA-COGEMA) reported non-significant positive risk coefficients for CeVD for the entire cohort [R5] and for the subset with adjustment for radon, external radiation, and medical heart disease risk factors [D24]. The German uranium miller study reported a non-significantly negative risk coefficient for LLR dose [K18]. In the study of French AREVA NC uranium processing workers, there was a statistically significant risk for Type S exposure to reprocessed uranium and a near-significant risk for Type M reprocessed uranium [G33], but little indication of risk from natural uranium exposure. Further, McGeoghegan et al. [M29] also reported an association between mortality from CeVD and radiation exposure in males performing industrial work in the BNFL cohort. Their analysis of internal exposure to any radionuclide gave a dose-response ERR per Gy of 1.47 (90% CI: 0.49, 3.00; n=456).

Table 20. Dose-response studies of uranium exposure and risk of circulatory system disease mortality

Study references	*No. of deaths*	*Nature of uranium work*	*Unit of uranium (LLR) exposure*	*Risk estimate per unit LLR exposure* [a]
ALL CIRCULATORY SYSTEM DISEASES				
Germany, Wismut [K14]	5 417	Mining	100 kBqh/m^3	ERR=–0.2 (95% CI: –0.5, 0.06)
France, CEA-COGEMA [R5]	185	Mining	kBqh/m^3	ERR=0.016 (95% CI: –0.06, 0.13)
France, CEA-COGEMA [D24]	76	Mining	kBqh/m^3	HR=1.13 (95% CI: 0.97, 1.31)
France, AREVA NC [G33]	111	Processing	Reprocessed uranium, absorption Types M, S	HR (95% CI) Cumulative exposure duration (per year): 1.09 (1.02, 1.18) [M] 1.11 (1.03, 1.20) [S] 1.04 (1.00, 1.07) for natural uranium [S] High cumulative exposure: 3.40 (1.47, 7.85) [M] 8.79 (1.21, 28) [S] 2.84 (1.38, 5.85) for natural uranium [S] Cumulative exposure score: 1.14 (1.05, 1.24) [M] 1.17 (1.07, 1.27) [S] 1.07 (1.02, 1.13) for natural uranium [S]
France, Gaseous diffusion [Z10]	281	Processing	Medium and high vs. no exposure	Natural soluble uranium compounds RR (95% CI): Medium RR=0.98 (0.71, 1.3) High RR=1.2 (0.85, 1.6) Enriched uranium (n=45): Medium RR=0.96 (0.32, 2.9) High RR=0.84 (0.28, 2.8) Depleted uranium (n=45): Medium RR=0.64 (0.23, 1.7) High RR=0.84 (0.32, 2.3)
HEART DISEASE				
Germany, Wismut [K14]	3 719 (all heart disease)	Mining	100 kBqh/m^3	ERR=–0.3 (95% CI: –0.6, 0.02)
France, CEA-COGEMA [R5]	72 (Ischaemic heart disease)	Mining	kBqh/m^3	ERR=–0.029 (95% n.e. (<0, 0.14)[b]
France, CEA-COGEMA [D24]	26 (Ischaemic heart disease)	Mining	kBqh/m^3	HR=0.94 (95% CI: 0.73, 1.20)
Germany [K18]	341 (Ischaemic heart disease)	Milling	100 kBqh/m^3	ERR=–0.09 (95% CI: –0.84, 0.65)

Study references	*No. of deaths*	*Nature of uranium work*	*Unit of uranium (LLR) exposure*	*Risk estimate per unit LLR exposure* [a]
France, AREVA NC [G33]	48 (Ischaemic heart disease)	Processing	Reprocessed uranium, absorption Types M, S	HR (95% CI) Cumulative exposure duration (per year) 1.08 (0.97, 1.21) [M] 1.14 (1.03, 1.26) [S] 1.04 (0.99, 1.10) for natural uranium [S] High cumulative exposure: 2.05 (0.53, 7.85) [M] 4.38 (0.47, 41) [S] 2.57 (0.82, 8.07) for natural uranium [S] Cumulative exposure score: 1.12 (0.99, 1.27) [M] 1.17 (1.03, 1.33) [S] 1.13 (1.05, 1.22) for natural uranium [S]
France, Gaseous diffusion [Z10]	95 (Ischaemic heart disease)	Processing	Medium and high vs. no exposure	Natural soluble uranium compounds (with 95% CI): Medium RR=0.71 (0.39, 1.3) High RR=0.91 (0.53, 1.5)
CEREBROVASCULAR DISEASE				
Germany, Wismut [K14]	1 297	Mining	100 kBqh/m^3	ERR=−0.05 (95% CI: −0.5, 0.6)
France, CEA-COGEMA [R5]	41	Mining	kBqh/m^3	ERR=0.125 (95% CI: −0.06, 0.50)
France, CEA-COGEMA [D24]	16[c]	Mining	kBqh/m^3	HR=1.17 (95% CI: 0.90, 1.53)
Germany [K18]	171	Milling	100 kBqh/m^3	ERR=−0.17 (95% CI: −1.14, 0.80)
France, AREVA NC [G33]	31	Processing	Reprocessed uranium, absorption Types M, S	HR (95% CI) Cumulative exposure duration (per year) 1.09 (0.93, 1.27) [M] 1.11 (0.95, 1.29) [S] 1.04 (0.97, 1.11) for natural uranium [S] High cumulative exposure: 5.71 (1.48, 22) [M] 3.26 (0.97, 11.0) for natural uranium [S] Cumulative exposure score: 1.13 (0.97, 1.31) [M] 1.16 (1.00, 1.35) [S] 1.01 (0.92, 1.12) for natural uranium [S]

Study references	*No. of deaths*	*Nature of uranium work*	*Unit of uranium (LLR) exposure*	*Risk estimate per unit LLR exposure* [a]
France, Gaseous diffusion [Z10]	77	Processing	Medium and high	Natural soluble uranium compounds (with 95% CI): Medium RR=1.2 (0.66, 2.3) High RR=1.07 (CI: 0.6, 1.9)

[a] Risk estimation metrics: ERR (excess relative risk) for which zero represents no excess or deficit; HR (hazard ratio) and RR (relative risk or rate ratio) are expressed as a multiple of the rate in the baseline (lowest/no exposure) group. (ERR = RR – 1).

[b] n.e. = not estimable from the likelihood profile.

[c] A case-control subset of workers for whom information was available on radon and external gamma exposure and medical risk factors. Risk estimates were adjusted for those factors.

279. Studies of CSD/IHD/CeVD end points typically had greater statistical power than those for most cancer diseases because the numbers of CSD-related deaths were much larger than for most types of cancer. Other considerations arise; one might expect lesser statistical power to detect CSD because the consensus has been that the risk coefficients derived for external radiation of the circulatory system are several times smaller than for cancer induction. On the other hand, damage to the kidney, which is thought to be a primary target organ for uranium, affects the risk of heart disease, probably through the renin-angiotensin pathway. Results regarding CSD end points are also difficult to interpret because of the numerous medical and lifestyle factors that affect cardiovascular risk. The results of the French processing workers (AREVA NC) suggesting that uranium compounds with low solubility may induce CSD more than soluble compounds are somewhat puzzling. While less soluble uranium compounds are thought to confer more risk to the lung because of longer residence times, it is believed that more soluble compounds confer larger doses to most other organs than insoluble compounds do because of differences in biokinetics. If so, the results of the French processing workers (AREVA NC) are contrary to what one would expect for CSD, IHD and CeVD.

(g) *Conclusion*

280. From the occupational exposure studies, a weak association of lung cancer risk with uranium exposure is concluded. However, currently available results are not consistent enough to demonstrate a causal association with uranium exposure. The results for leukaemia, other lympho-haematopoietic malignancies, digestive system cancers, kidney and other urological cancers and brain/CNS tumours did not provide clear evidence of uranium exposure-related risks. The results for non-malignant diseases—respiratory, cardiovascular and kidney diseases—also showed no relationship with uranium exposure. A number of studies without dose-response analyses for LLR exposure have provided null overall risk estimates for every health end point considered; while the negative SMRs are not very specific, at least they suggest the risks are likely to be small.

5. Limitations of occupational exposure studies

281. For uranium miners studies, recent developments enabled the calculation of organ doses and, therefore, estimation of the contribution of LLR from uranium ore. Studies published up to now have demonstrated a very small contribution of uranium to miner dose. Organ doses appear to be dominated by radon and radon decay products for lungs and by external gamma exposure for other organs. Demonstrating a potential risk associated to uranium, therefore, appears difficult.

282. Studies of uranium millers are limited in size, with the exception of the German Wismut miller study, which allowed assessment of individual radiation doses from uranium exposure [K18]. Undertaking analysis of combined cohorts after further development of organ dose calculation should improve results in the future.

283. Most studies of workers in the nuclear fuel cycle are limited by the difficulties in estimating the doses due to uranium internal contamination. Recent studies are the most meaningful since they have been based on more accurate exposure assessment and for some of them internal organ-specific absorbed doses were estimated by implementing the latest updates of the ICRP models and dosimetric tools. Nevertheless, improvement of dosimetric estimation is still needed to provide pertinent estimates of potential risks associated with uranium contamination. Segmentation between the different steps of the nuclear fuel cycle should enable improved assumptions regarding the solubility of the uranium compounds. The combined use of individual urinalysis dosimetry and of job exposure matrices may also allow improved characterization of radiation doses from uranium exposure and the quantification of related risks.

284. Natural uranium is not very radioactive (^{238}U decays very slowly) and its chemical properties are often such that any inhaled or ingested uranium is excreted rather quickly from the human body. Thus, studies of exposure to enriched or reprocessed uranium may be more informative. Some publications indicated that—even when the uranium doses are known—external exposure can dominate [L24]. In addition, most of these studies had major limitations (poor statistical power, no or imprecise estimates of doses, insufficient accounting for other exposure influences). Moreover, other exposure is mostly not taken into account, such as exposure to chemicals, heat and noise, which may also contribute to the increase of certain diseases.

285. Uranium worker data have often been limited to studies of male Caucasians. Quantitative generalization to women or other population groups is therefore uncertain. No occupational studies have attempted to examine genetic, epigenetic or metabolic susceptibility factors for uranium related diseases. Worker studies also provide no information about children, who may be more susceptible to the effects of uranium exposure than adults.

286. Continued follow-up of the principal uranium worker cohorts that have individualized worker exposure data will be valuable. Many members of the cohorts were relatively young at their most recent follow-up. Because mortality rates for many cancers increase as a power of age attained, these cohorts will become increasingly informative with future follow-up, providing greater ability to detect smaller effects and generate more precise risk estimates.

287. Since most studies have a limited number of uranium workers and relatively slight exposure for most of the workers, it is unlikely that epidemiological studies of individual nuclear facilities will have sufficient statistical power for a reasonable prospect to detect risks. Consequently, international pooled studies with high-quality, harmonized individual exposure estimates are likely to be necessary to assess uranium risks with high precision. However, studies of workers have advantages over those on environmental exposure of the public or of special groups (e.g. military personnel deployed in regions with potential DU exposure). The advantages particularly centre around having measurements to estimate individual uranium exposure levels, along with other occupational radiological exposure so they can potentially distinguish LLR exposure from other exposures. In addition, some of the studies had data on various chemical exposure at workplaces.

B. Studies of Gulf War veterans

288. Depleted-uranium munition and armour were extensively used by the United States military in the first Gulf War in Iraq and Kuwait (Desert Storm) and again in the Balkans military action. Military personnel were exposed to DU via inhalation or wounds, notably due to friendly-fire incidents burning depleted-uranium-containing tanks and ammunition and clean-up operations [B26].

289. Several authors reported investigations on the Gulf war and the Balkan veterans, especially on United States, United Kingdom, Canadian, Danish and Dutch veterans [B28, M1, M2, S36, U11], which were reviewed by others [I20, L5, S6]. For example, the Institute of Medicine [I20] discussed extensively the results of about 25 studies on health outcomes following exposure to natural uranium and DU. The review integrated malignant (lung cancer, leukaemia, Hodgkin's and non-Hodgkin's lymphoma, bone cancer, renal cancer, bladder cancer, brain and other nervous system cancers, stomach cancer, prostatic cancer, testicular cancer) and non-malignant (renal disease, respiratory disease, neurological effects, reproductive and developmental effects, cardiovascular effects, genotoxicity, haematological effects, immunological effects, and skeletal effects) pathologies. They concluded that there was insufficient evidence to determine whether an association exists between exposure to uranium and the health outcomes cited above. However, the two following major limitations of the veteran studies were identified: (*a*) short period of follow-up and (*b*) poor assessment of uranium exposure.

290. The Royal Society comprehensively reviewed the use of DU, especially on the battlefield [R28]. The Royal Society concluded in its report that doses from DU were unlikely to be high, even in the most unfavourable (battlefield) conditions, so that lung cancer risks were unlikely to be more than doubled. The report indicated a potential non-radiological risk associated with exposure to DU, in particular with its nephrotoxicity. A summary of studies of the health status of veterans with potential or known exposure to DU is given in appendix A, table A5.

291. A recent study by Strand et al. aimed to investigate cancer incidence and also all-cause mortality in a cohort of Norwegian military present in Kosovo between 1999 and 2011 [S42]. Cancer incidence and mortality were studied from 1999 to 2011 and compared to national rates. The authors found no excess incidence of cancer except an elevated SIR for melanoma of the skin in men. All-cause mortality was half the expected rate (SMR=0.49; 95% CI: 0.35, 0.67).

292. A biennial health surveillance programme established for the United States Gulf War veterans has shown continuously elevated DU concentrations in urine among those with embedded fragments for over 20 years [M25]. No differences have been seen between the high- and low-exposure groups with regard to haematology, clinical chemistries, neuroendocrine parameters, bone metabolism, neurocognitive function, immune function, pulmonary function or nodules. Regarding renal function and injury, no high vs. low exposure differences were found for 16 clinical indicators of renal function, six urine markers for kidney injury, or four urine measures of low molecular weight proteins, except for two sensitive biomarkers of proximal tubule function that suggested subtle renal injury [M25].

293. In a study by Hines et al., some self-reported respiratory symptoms, mean pulmonary function values and prevalence of low-dose chest computed tomography abnormalities were compared in two populations of Gulf War veterans (high body burden group vs. low body burden) [H18]. The authors found no significant differences between the two groups, suggesting that DU levels inhaled during the 1991 fire incidents probably do not cause long-term adverse pulmonary health effects [H18].

294. In conclusion, several studies on the health pathologies among veterans with potential or no exposure to DU were published. Up till now, no clinically significant pathology related to DU has been found in the veteran's cohorts. The diversity of these studies in terms of topics has limited their

reproducibility, except for the biennial examinations of a small group of United States veterans with retained DU shrapnel in whom comprehensive examinations have consistently found no clinically adverse effects.

C. Studies of environmental exposure

1. Living around uranium processing facilities

295. Numerous, mostly ecological, studies have been carried out to assess whether long-term residence in the vicinity of nuclear fuel cycle facilities or nuclear power plants affects the health of the residents. To focus on uranium effects, only studies carried out in population groups living around uranium processing facilities (after uranium mining and prior to electricity production) were examined. Eleven published studies were identified over the past ten years, which are presented in appendix A, table A6.

296. Because of potential bias, inability to check the validity of ecological results, and the lack of sufficient measurements of ambient uranium exposure levels, no firm conclusion could be drawn from ecological studies. Further, caution is required in interpreting ecological studies in general as causal inference is not warranted because of numerous limitations in their study design. The major limitation of ecological studies is the potential of ecological associations to misrepresent, sometimes greatly, the biological effect at individual level. Thus, an association observed between variables on an aggregate level does not necessarily mean that the same association will exist at individual level [G19].

297. Lane et al. reported a review of 13 epidemiological studies conducted in Port Hope, Canada in the past 30 years, including residents and workers [L7]. These studies included environmental measurements of the radiological and non-radiological contaminants, the estimation of the multi-pathway of exposure and also the health risks to the population, using environmental monitoring data or dose reconstruction methods based on a variety of approaches. The authors concluded that, taken together, the findings of these studies conducted on the Port Hope community indicated that observed adverse health effects were unlikely to be the result of exposure to environmental contaminants from radium and uranium processing. Other studies shown in appendix A, table A6 are also consonant with that conclusion.

2. Living in an environment affected by depleted uranium munition use

298. Some epidemiological studies attempted to determine if the health of populations living in countries or regions involved in the recent conflicts (i.e. Iraq, Kuwait, Bosnia and Herzegovina, Kosovo, Serbia and Montenegro) was affected by the use of DU in shrapnel or tanks. Iraq is the most studied country for investigation on possible effects of DU. Several publications aimed at describing the incidence and types of congenital malformations [A6, A7, S48] or birth defects [A3, B54, F1]. However, these publications failed to demonstrate a link between the increase in these pathologies and the environmental exposure to DU, notably due to the absence of evaluation of the exposure levels.

299. Few studies investigated cancer incidence in these populations. Al-Hashimi and Wang used in their study three sub-periods (1980–1990, 1991–2000, and 2001–2010), corresponding to the three Iraq wars, the Iran–Iraq war (1980–1988), the Gulf War I in 1991 and the Gulf War II in 2003 [A4]. The authors reported increases in the total number of cancer cases. However, the in-depth analysis indicated

a decrease in incidence rates in most cancer types when they were analysed statistically, considering population growth in the Ninawa province in the northern part of Iraq.

300. Another study aimed to describe changes in haematological malignancies (leukaemia and Hodgkin's lymphoma) in Croatian counties potentially exposed to DU in comparison to the pre-war period [L3]. This study did not find a significant difference in the incidence of these haematological malignancies.

301. In parallel to these health studies, measurements were made of daily urinary uranium excretion in German peacekeeping personnel (n=1,228) and unexposed subjects coming from the South of Germany (n=113) to assess potential intakes of DU [O1]. A daily urinary excretion of uranium of 13.9±2.2 ng/day (3 to 23 ng/day) measured for German peacekeeping personnel was similar to that of unexposed subjects (12.8±2.6 ng/day).

3. Drinking water with elevated uranium levels

302. Possible health effects after long-term ingestion of uranium via drinking water was reviewed by Guseva Canu et al. [G32]. The description and main results for selected studies of the possible impact of elevated levels of uranium in drinking water are summarized in appendix A, table A7. This table notes potential uranium effects ascribable to its dual radiological and chemical toxicity. However, some studies related the effects to chemical toxicity only [K26, K27, K28, M9, S8, Z6], while other studies related to potential radiation effects [A32, K29, S7].

303. As shown in appendix A, table A7, most of the studies focused on the nephrotoxicity of uranium using cross-sectional study designs. In total, five studies were carried out: in Canada [M9, Z6, Z8]; in Finland [K26]; and in Sweden [S8]. The uranium concentrations in water were fairly similar in all the studies, with median concentrations in the range 20–30 µg/L among the exposed groups. All these studies, except the one from Mao et al. [M9], found no glomerular effect of chronic ingestion of uranium. Among people drinking water from private drilled wells, uranium exposure caused damage to the proximal tubule, shown by nephron reabsorption alteration [K26, S8, Z6] or tubular cytotoxicity [S8, Z1] was observed in four of the studies. Several biomarkers were measured in these studies (e.g. creatinine for glomerular filtration function at the early stage of renal injury) but none was specific for injury caused by uranium. Kurttio et al. [K29] carried out a case–cohort study in Finland of bladder and kidney cancer after long-term consumption of private well water containing uranium and its decay products. No association between the prevalence of these cancers and the uranium concentration in well water was found [K29].

304. Lymphatic and haematopoietic malignancies were considered in three studies [A32, S7, W23]. Seiler [S7] investigated whether 16 children with leukaemia in the City of Fallon, Nevada, United States, had higher levels of naturally occurring radioactive material in their well water compared to other inhabitants of the town. Water samples were collected in 2001 for the measurement of uranium, radon and gross alpha concentrations, and leukaemia cases were identified for 1997–2000. To resolve this potential time sequence problem, the authors also retrieved the 1989 citywide water analyses. The natural origin of the uranium present was confirmed by the calculation of the isotopic ratio. No difference was indicated in uranium concentration in the water drunk by the children compared to other inhabitants.

305. Witmans et al. [W23] compared the uranium concentrations in water between non-Hodgkin's lymphoma cases and their matched controls selected from the Saskatchewan (Canada) cancer registry. The cases had been exposed to significantly higher uranium concentrations in drinking water than the controls. However, uranium was one of 63 inorganic constituents tested in the study.

306. A case–cohort study by Auvinen et al. [A32] of Finnish adults that enrolled 35 cases of leukaemia also reported a negative result regarding exposure to naturally occurring uranium (and its decay products) in drinking water and leukaemia [A32]. The statistical power of the study was limited and no data on potential confounding factors were available. The risk of stomach cancer from exposure to naturally occurring radionuclides in drinking water was investigated. However, no association was found in this study.

307. Clinical studies in Nova Scotia, Canada performed on 324 persons exposed to variable amounts of naturally occurring uranium in drinking water (up to 0.7 mg/L) found no relationship with overt renal disease. Though there was a trend towards increasing excretion of urinary β-2 microglobulin with increasing concentration of uranium in well water, this was not seen in the group with the highest uranium well-water concentrations. This group had significantly reduced its consumption of well water by the time the measurements were made, supporting the hypothesis that the suspected tubular defect might well be rapidly reversible [M64, M65].

308. A pilot study by Mao et al. of three communities in Saskatchewan with mean uranium levels ranging from 0.71 (control) to 19.6 μg/L found a statistically significant association (p=0.03) between increasing but normal levels of urine albumin and the uranium exposure [M9]. Another Canadian study on two groups of subjects with chronic exposure to uranium in drinking water, the first group exposed to <1 μg/L and the other exposed to 2–781 μg/L found no correlation with alkaline phosphatize and β-2 microglobulin in urine. The authors concluded that the uranium concentrations observed in the study affected the kidney function at the proximal tubule [Z6].

309. Another study by Zamora et al. [Z8] on chronic ingestion of uranium in drinking water demonstrated subtle changes in two of the indicators measured that were statistically significant—namely, glucose and LDH excretion concentrations. However, this did not result in any observable health effects (see also table 13). In addition, the change in LDH excretion was rather beneficial and was seen only in males. Thus, these changes are not nephrotoxic effects.

310. In conclusion, epidemiological studies of public uranium exposure to drinking water indicate that chemical toxicity of uranium may occur mainly in the kidneys and, in high concentrations, uranium may affect the kidney function. However, the functional alterations found in the kidneys were small and within normal limits, so the clinical significance of the findings may be minimal. The available literature focused on lymphatic and haematopoietic tissue malignancies is limited to three studies, which do not support a causal association between uranium exposure and those malignancies.

IX. RESEARCH NEEDS

311. The estimation of organ doses from incorporated uranium isotopes depends on the availability of reliable biokinetic data and the construction of physiologically realistic biokinetic models. In general, good human and animal data are available for the construction of models. However, limited information is available on the age-dependence of organ retention and excretion rates, including information on the cross-placental transfer of uranium. In addition, more information is required on the distribution of uranium within tissues and cells, for example in CNS tissue and lungs.

312. Dosimetric models in general apply the same assumptions regarding source and target distributions within tissues to all internal emitters. For example, uranium isotopes and other radionuclides deposited in bone are assumed to accumulate on internal bone surfaces and/or in bone volume and target cells for cancer induction are assumed to reside along bone surfaces (bone cancer) and throughout red bone marrow (leukaemia). The validity of such assumptions requires further investigation, with consideration of the inhomogeneity of uranium distribution within tissues and cells.

313. Toxicological studies of uranium exposure are required to distinguish the chemical and radiological components of damage caused to cells and tissues, including short-term damage to organ function and longer-term effects including cancer. Comparisons of radionuclide toxicity and RBE determinations would assist in quantifying the potential health effects of uranium isotopes. Studies of the age-dependence of chemical and radiological toxicity would be valuable.

314. Future epidemiological studies require careful consideration of the acquisition of dosimetric data to assess individual organ and tissue doses for cohort subjects. A high priority would be a consortium effort by investigators to develop pooled data on uranium risks. The result could be considerable gains in the statistical power and precision of risk estimates that would potentially provide the best overall answers achievable as to health effects from uranium exposure. Pilot studies to quantify the magnitude of uncertainties in exposure assessment would ideally be part of this effort, so that sound estimates of dosimetric uncertainties could be incorporated into the risk modelling [L13, S21].

315. Concerning (molecular) epidemiology, setting up prospective follow-up or case control studies in selected subgroups, including collection of information on biomarkers, has the potential to provide more specific dose–response curves for defined subsets of cohorts and thereby improve knowledge of health effects in humans, including cancer and non-cancer diseases. High-throughput technologies (especially the -omics) would be relevant to apply to this field. However, proposed biomarkers will need to be rigorously evaluated as to their ability to improve exposure and risk assessment.

316. Mixed exposure should be taken into account when studying effects, such as other radionuclides (e.g. ^{239}Pu, ^{222} Rn), other chemical carcinogens (e.g. solvents, smoking, dust, silica, asbestos) and also the physical forms of uranium (solubility), e.g. through further development of exposure matrices in epidemiological research, and through animal studies.

317. Understanding the molecular mechanism of action of uranium on cells in culture and animal models, both as a metal and as a radionuclide, would be important in (*a*) facilitating the identification of bioindicators; (*b*) identifying portions of the molecular response that are attributable to the radiation response, the heavy metal response or both; and (*c*) defining the possible development of mitigators, (few mitigators for uranium exposure).

X. GENERAL CONCLUSION

318. This annex provides a detailed review of sources and levels of uranium in the environment, exposure of the public and workers to uranium, biological effects of uranium, and epidemiological studies of nuclear workers and the public exposed to uranium.

319. Uranium is a naturally occurring radionuclide and is ubiquitously distributed in the environment. In daily life, people are exposed to uranium originating mainly from drinking water and foodstuffs. Average uranium levels in water vary between countries and within countries, with typical values of around 2 μg/L (~25 mBq/L of ^{238}U) in groundwater and 1 μg/L (~12.4 mBq/L of ^{238}U) in public water supplies. Some drinking water samples (<3%) may exceed the national or international guidelines set to prevent kidney toxicity. Concerning foodstuffs, potatoes, meat, fresh fish and bakery products are the main sources of uranium ingestion. The total daily intake from water and food consumption is around 1.5 μg/d (18.6 mBq/d of ^{238}U).

320. The main routes of entry of uranium into the body are inhalation and ingestion. The absorption to blood in each case is highly dependent on the chemical form (speciation) of the intake. For example, human data show that the absorption of ingested uranium is a few per cent of intake for soluble forms in water compared with substantially less than 1% for insoluble oxides. Human and animal data have been used to model the behaviour of uranium absorbed to blood, showing that the main site of retention is the skeleton, with lower amounts in soft tissues and rapid urinary excretion of a large proportion. The ICRP models make appropriate use of the available data.

321. Uranium is both a radioelement and a metal, and biological effects may result from the combined effects of the chemical element or species and the radiation. The radiological and chemical consequences of internal exposure to uranium depend partly on the route of intake (principally inhalation or ingestion), and the chemical form of the intake. Some effects are likely to be related to the chemical toxicity of uranium species, namely the renal effects, whereas others are rather related to radiological toxicity of uranium, including tumorigenic effects such as soft tissue sarcomas in rats and osteosarcoma in mice. In general, chemical effects are observed with short lag-times after exposure whereas radiological effects such as carcinogenesis have long lag-times.

322. Considering the chemical effects of uranium species, the kidneys are the most sensitive target organ. At higher levels, chemical effects of uranium are also observed in bones, indicating that uranium can induce effects on bone metabolism such as the impairment of bone growth and formation. Chemical effects of uranium have also been observed, in rodent studies, in liver, gonads, central nervous system, and the immune system. These experimental studies indicate that uranium induces biological effects in these organs, but the changes do not lead to the appearance of observable pathologies. While effects in these tissues may be seen at higher doses, damage to kidneys (and skeleton) is likely to be critical. Concerning the central nervous system, animal studies suggest that high doses of uranium may have some negative effects on the behaviour of animals. With the exception of kidney damage, animal studies showing toxicological effects have used concentrations of uranium substantially above those to which humans are exposed. No clinically significant pathologies have been found in the veteran cohorts potentially exposed to DU. Moreover, the biennial examinations of a group of United States veterans with retained DU shrapnel have found no clinically meaningful adverse effects.

323. Epidemiological studies of uranium miners and millers have included estimates of doses, showing the small contribution of uranium to overall doses and the dominant contributions of radon and radon decay products to lung dose and external gamma radiation for other organs. Most studies of nuclear workers are limited by difficulties in estimating radiation doses due to uranium. A weak association of lung cancer risk with uranium exposure is suggested but the currently available results are not

consistent enough to demonstrate a causal association. Results for other malignancies and non-malignant disease were also negative. The Committee concluded that epidemiological studies of public exposure to uranium in drinking water have reported small functional alterations in the kidneys, within normal limits and hence of minimal clinical significance.

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APPENDIX A. TABLES SUMMARIZING URANIUM LEVELS IN WATER, STUDIES OF OCCUPATIONAL AND ENVIRONMENTAL EXPOSURE TO URANIUM

Tables A1 to A4 present uranium levels in water.

Tables A5 to A8 present four groups of occupational studies that provide increasing levels of information on uranium-specific risks.

Tables A9 to A11 present studies of risks from various sources of potential military and environmental exposure to uranium.

Table A1. Overview of uranium content in groundwater worldwide

The numbers in italics correspond to calculated data obtained from the mass activity of natural uranium of 25,400 Bq/g and from the relative proportion of ^{238}U (12.4 mBq/µg) in natural uranium of 48.3%; * mean value (not median value); n.i: information not included in the study

Continent	*Country*	*Location*	*Sample number*	*Total uranium (µg/L)*	*^{238}U (mBq/L)*	*Reference*
Europe	Finland	n.i.	396	0.15 (<0.01–10)	*1.84 (0.12–123)*	[T22]
	Finland	South	13	285 (5.6–3 410)	*3 504 (143–41 924)*	[P28]
	Finland	South	288	1.5 (0.3–800)	19 (4–9 990)	[V4]
	Finland	South	194	28 (0.001–1 920)	*344 (0.01–23 605)*	[K26]
	Finland	South	167	2 (<0.01–1 770)	*24.6 (<0.12–21 761)*	[M67]
	Sweden	Värmland	153	6.7 (<0.20–470)	*82.4 (<246–5 778)*	[S8]
	Sweden	South	328	*14.2 (<2–425)*	177 (<27–5,293)	[I22]
	Norway	South	476	2.5 (–750)	*31 (–9 300)*	[F12]
	Poland	Swieradow	51	*1.26 (0.2–2.4)*	15.55 (2.4–29.4)	[K10]
	Spain	Catalonia	37	*4.88 (<0.41–56.1)*	60 (<5–690)	[O8]
	Switzerland	n.i.	5 548	0.77 (0.05–92.02)	*9.5 (0.61–1 131)*	[S33]
	France	Vals les Bains	n.i.	1.85 (0.55–3.6)	*22.7 (6.8–44.3)*	[M34]
	Greece	North	10	2.02 (0.15–7.66)	25.06 (1.82–95.3)	[S1]
North America	Canada	n.i.	n.i.	0.31 (0.16–6.23)	*3.8 (2.0–76)*	[L12]
	Canada	Kitigan Zibi, Quebec	32	39.25 (0.4–845.33)	*470 (4.9–10 392)*	[Z8]
	Canada	Southeastern Manitoba	287	10 (<0.02–2 020)	*124 (<0.25–25 048)*	[B21]
	Canada	Nova Scotia	20	0.39 (0.06–41.08)	*4.8 (0.8–505)*	[K19]
	USA	Connecticut	11	16.3 (0.21–1 166)	*200 (2.6–14 335)*	[M5]
	USA	Connecticut	35	157 (1.8–7 780)	*1 930 (22.1–95 649)*	[O5]
	USA	Cities with the largest average concentration	55 433	*1.04 (0.03–1 945)*	12.95 (0.37–24 124)	[C34]
South America	Brazil	Sao Paulo et Santa Catarina	78	*0.28 (0.008–15.0)*	3.4 (0.1–184.3)	[B43]
	Brazil	n.i.	358	1.2* (<0.01–7.5)	*14.8 (0.12–92.2)*	[G14]

Continent	*Country*	*Location*	*Sample number*	*Total uranium (μg/L)*	*^{238}U (mBq/L)*	*Reference*
Africa	Morocco	n.i.	15	*4.5 (0.37–25.1)*	55 (4.5–309)	[H4]
	Ethiopia	Rift Valley	138	0.55 (0.005–48)	*6.8 (0.06–590)*	[R10]
	Egypt	Eastern desert	12	5.21 (1.19–519.4)	*64.1 (14.6–6 386)*	[D2]
	Ghana	North and coast	195	0.114 (<0.001–1.99)	*1.4 (<0.01–24.4)*	[R23, Z16]
Asia	Fujian Province	China	110 and 552	0.54 (0.03–13.4)	*6.6 (0.4–164)*	[Z16]
	Iran	Caspian Sea	27	*2.2 (0.24–5.4)*	27 (3–66)	[J5]
	Jordan	n.i.	n.i.	1.3 (0.5–6.7)	*16.0 (6.6–82.4)*	[V3]
	Bangladesh	West	67	2.5 (0.2–10)	*30.7 (2.5–25.8)*	[F14]
	Japan	Niigata	23	*0.001 (0.0005–0.03)*	0.018 (0.005–0.383)	[T14]
	India	Hisar	38	33.9* (5.3–113.5)	*417 (65.2–1 395)*	[G3]
	India	Kula area	15	0.83 (0.26–2.56)	*10.2 (3.2–31.5)*	[S27]
	India	Punjab	25	22 (2.65–74.98)	*271 (32.6–922)*	[K22]

Table A2. Overview of uranium content in surface water worldwide

The numbers in italics correspond to calculated data obtained from the mass activity of natural uranium of 25,400 Bq/g and from the relative proportion of ^{238}U (12.4 mBq/μg) in natural uranium of 48.3%; n.i: information not included in the study

Continent	*Country*	*Location*	*Sample number*	*Total uranium (μg/L)*	*^{238}U (mBq/L)*	*Reference*
Europe	Finland	Southern Finland	184	0.18 (0.08–34)	2 (1.0–420)	[V4]
	Finland	n.i.	152	0.099 (<0.01–0.92)	*1.2 (<0.12–11.3)*	[T22]
North America	USA	Cities with the largest average concentration	34.561	*0.45 (0.03–1 737)*	5.55 (0.37–21 534)	[C34]
South America	Argentina	n.i.	92	1.9 (<0.01–50)	23.4 (<0.12–615)	[B41]
Asia	India	Upper Siwaliks and Punjab	34	3.84 (1.08–19.68)	*47.2 (13.3–242)*	[S23]
	Iran	Ardabil	22	4.2 (2.1–13.6)	*51.6 (25.8–167)*	[H2]

Table A3. Overview of uranium content in public water supplies worldwide

The numbers in italics correspond to calculated data obtained from the mass activity of natural uranium of 25,400 Bq/g and from the relative proportion of ^{238}U (12.4 mBq/µg) in natural uranium of 48.3%; * mean value (not median); n.i: information not included in the study

Continent	*Country*	*Location*	*Sample number*	*Total uranium (µg/L)*	*^{238}U (mBq/L)*	*Reference*
Europe	Finland	Southern Finland	951	1.25 (<0.01–1 770)	*15.4 (<0.12–21 761)*	[M67]
	Germany	Bavaria	461	0.9 (<0.01–39)	*11.1 (<0.12–479)*	[R3]
	Germany	National scale	564	3.2 (<0.7–320)	*39.3 (8.6–3 934)*	[B23]
	Germany	National scale	164	0.073 (0.00115–9.0)	*0.90 (0.001–111)*	[B24]
	Germany	National scale	36	*2.0 (<0.16–60.2)*	24 (<2–740)	[G2]
	Austria	n.i.	41	0.91 (0.06–79.2)	11.2 (0.72–975)	[G6]
	Austria	Waldviertel	48	1.1 (0.1–57.5)	14.05 (0.7–707)	[W5]
	Greece	Aksios, Kalikratia	23	3.46 (0.061–10.02)	*42.5 (0.75–123)*	[K7]
	Poland	Centre	26	*0.39 (0.03–1.94)*	4.8 (0.4–23.9)	[P20]
	Spain	Biscay	4	*0.07 (0.003–0.24)*	0.8* (0.04–2.9)	[H17]
	Italy	Rome	9	*1.46 (0.02–8.37)*	18 (0.3–103)	[J2]
	Norway, Sweden, Finland, Iceland	Several places	22	0.107 (0.0049–56.2)	*1.32 (0.06–691)*	[F13]
North America	USA	Illinois, Minnesota, Texas, Wisconsin	24	0.25 (0.1–13.2)	*3.1 (1.23–162)*	[L50]
South America	Argentina	12 provinces	145	0.4 (<0,01–21)	*4.9 (<0.12–258)*	[B41]
Africa	Morocco	National scale	6	*0.75 (0.20–1.28)*	9.25 (2.5–15.7)	[H4]
Asia	Islamic Rep. of Iran	Ardabil	3	7.6 (4.7–11.7)	*93.4 (57.8–144)*	[H2]
	India	Punjab		3.84 (1.11–19.68)	*47.2 (13.6–242)*	[S22]
	India	Punjab	45	10.4 (1.24–45.42)	260 (30–1 150)	[R8]
	India	Punjab		29 (2.5–313)	*357 (30.7–3 848)*	[S11]
	India	Himachal Pradesh	46	1.34 (0.56–10.11)	30 (10–260)	[R8]
	India	Western Haryana	23	17.03 (6.37–43.31)	*209.4 (78.3–532)*	[K1]
Oceania	Australia	West	23	*0.19 (0–1.16)*	2.3* (0–14.3)	[W7]
	Australia	West	173	0.06* (<0.001–1.40)	*0.74 (<0.01–17.2)*	[C1]

Table A4. Overview of uranium content in bottled mineral water worldwide

The numbers in italics correspond to calculated data obtained from the mass activity of natural uranium of 25,400 Bq/g and from the relative proportion of ^{238}U (12.4 mBq/µg) in natural uranium of 48.3%; * mean value (not median); n.i: information not included in the study

Continent	*Country*	*Sample number*	*Total uranium (µg/L)*	*^{238}U (mBq/L)*	*Reference*
Europe	Germany	908	0.17 (<0.0005–16.0)	*2.09 (<0.006–197)*	[B24]
	Germany	21	*0.41 (<0.08–11.4)*	5 (<1–140)	[G2]
	Spain	32	*0.48 (0.04–5.8)*	5.9 (0.5–70.9)	[D14]
	Slovenia	11	*0.42 (0.09–4.3)*	5.2 (1.1–53)	[B13]
	Italy	21	*1.38 (0.20–9.92)*	17 (2.5–122)	[R30]
	Italy	51	*0.73 (<0.01–7.2)*	8.97* (<0.17–89)	[D11]
	Poland	22	*0.59 (0.06–0.86)*	7.26 (0.75–10.54)	[C19]
	Croatia	12	*0.53 (0.17–1.19)*	6.55 (2.1–14.6)	[R29]
	France, Portugal, Spain	14	*3.58 (1.79–40.7)*	44 (22–500)	[M14]
	France	106	0.2 (<0.10–19)	2.25 (<1.3–230)	[A27]
	28 countries	132	0.23 (0.0002–27.5)	*2.8 (0.002–338)*	[K11]
	Austria	10	0.16 (0.012–5.4)	*2.0 (0.15–66.4)*	[W4]
	Norway, Sweden, Finland, Iceland	n.i.	0.102 (0.0055–32.4)	*1.25 (0.07–698)*	[F13]
South America	Argentina	62	1.9 (0.04–11)	*23.4 (0.5–135)*	[B40]
Africa	Tunisia	10	*1.01 (0.13–2.14)*	12.36 (1.56–26.36)	[G7]
	Morocco	10	0.54 (0.34–0.70)	6.6 (4.2–8.6)	[M48]
Asia	Kuwait	23	*0.22 (0.05–2.04)*	2.74 (0.63–25.07)	[A11]

Table A5. Studies of workforces that include workers (potentially) exposed to uranium though not explicitly identified

Study references	*Summary of study*	*Summary of findings relating to uranium*	*Relevance for this report*
Atkinson et al. [A29]	UKAEA employees, 1946–1996. 10,249 deaths. Dosimetry: external radiation doses. Neutron and tritium doses included when available. Internal doses noted but not quantitative	All cancer: external radiation exposure trend tests in those monitored for any internal exposure. Trends not significant for all cancer, stomach, colon, liver, pancreas, lung, bladder, kidney, brain Prostate cancer: dose-response trend before 1980, but not 1980–1997 among those with internal monitoring, but uranium not examined	Not possible to derive uranium-specific risks, because uranium workers not analysed separately, and uranium-specific doses not used
Atkinson et al. [A30]	Further analysis of an extended UKAEA dataset [A29], conducted by time period to examine internal exposure for pre/post 1980 and prostate cancer. Excess associated with work with heavy-water reactors. Radionuclides of concern: ^{3}H, ^{59}Fe, ^{51}CR, ^{60}Co, ^{65}Zn. Case-control prostate cancer substudy conducted	Prostate cancer: exposure levels at heavy-water reactors fairly constant over time, but no indication of elevated risk after 1980. So earlier excess with internal exposure probably not meaningful	Not possible to derive uranium-specific risks, because uranium workers not analysed separately, and uranium-specific doses not used
Carpenter et al. [C8]	Cancer mortality 1946–1988 among 75,006 UKAEA, AWE and BNFL employees. Uranium exposure not assessed	All cancer: analyses of external radiation plus tritium exposure	Not possible to derive uranium-specific risks, because uranium workers not analysed separately, and uranium-specific doses not used
Carpenter et al. [C9]	Cancer mortality 1946–1988 among 40,761 UKAEA, AWE or BNFL employees who had radionuclide monitoring	All cancer: separate analyses conducted for tritium, plutonium and other radionuclides. Insufficient detail about other radionuclides, so no uranium analyses	Not possible to derive uranium-specific risks, because uranium workers not analysed separately, and uranium-specific doses not used
Cragle et al. [C36]	Savannah River Plant (USA) conducted uranium processing, nuclear fuel fabrication and processing. Follow-up to 1980, 9,860 white male employees. 85% of exposure to external radiation; exposure to numerous internal radionuclides	Analyses by time of first employment and years of employment. Suggestion of elevated leukaemia risk in small subgroup of early workers, but uranium exposure not reported	Not possible to derive uranium-specific risks, because uranium workers not analysed separately, and uranium-specific doses not used
Fraser et al. [F10]	Cancer mortality and morbidity in UKAEA cohort of 39,718 during 1946–1986. Internal exposure noted for tritium, plutonium or other unspecified radionuclides	Cancer analyses conducted for external exposure, tritium, plutonium and "monitored for any radionuclide"	Not possible to derive uranium-specific risks, because uranium workers not analysed separately, and uranium-specific doses not used
Loomis and Wolf [L44]	Cancer mortality (1947–1990) among 6,591 white males at USA Oak Ridge Y-12 nuclear material production plant. Plant converted UF_6 to UF_4 to uranium metal which was fabricated and milled. Other exposure: beryllium, solvents, machine oils, mercury, lead	No measurements or estimates of uranium exposure, so no relevant analyses	Not possible to derive uranium-specific risks, because uranium workers not analysed separately, and uranium-specific doses not used
McGeoghegan and Binks [M28]	Mortality and cancer morbidity in 2,209 radiation workers at UK Chapelcross plant, 1955–1995. Main activity: operation of 450 MW Magnox gas cooled reactors	No measurements reported of internal exposure: only external radiation analysed	Not possible to derive uranium-specific risks, because uranium workers not analysed separately, and uranium-specific doses not used
McGeoghegan et al. [M29]	38,779 radiation and 15,040 non-radiation male workers at UK BNFL facilities (Sellafield, Springfields, Capenhurst, Chapelcross). Some workers had exposure to uranium, plutonium, tritium and other radionuclides	Investigated circulatory and other non-cancer diseases. No measurements of internal exposure, analysed external radiation exposure only	Not possible to derive uranium-specific risks, because uranium workers not analysed separately, and uranium-specific doses not used

Table A6. Studies of groups of workers identified and investigated as uranium workers but not monitored specifically for potential exposure to uranium, so uranium-specific doses were not available

Abbreviations: LLR, long lived radionuclide exposure, primarily from uranium

Study references	*Summary of study*	*Summary of findings relating to uranium*	*Relevance for this report*
Baysson et al. [B9]	Metallurgy department workers (N=356) of French CEA, 1950–1968 were studied for excess cancers (1950–1990), since workers believed there was a cancer cluster. Department research primarily on uranium metallurgy. Reconstructed external radiation doses; internal radionuclide and chemical exposure noted. Radionuclides: thorium, natural uranium/enriched uranium, some activation and fission products	255 handled radionuclides, principally natural uranium, mean exposure duration 11 years All cancer: suggestion of risk (p=0.13) per year handling radionuclides, but stronger trend for handling chemicals Multiple myeloma: suggestive excess, but only 2 cases (0.2 expected, SMR=8.4, 90% CI: 1.4, 26). No evidence of cancer cluster	Study small, low statistical power. Analysis only for exposure to any radionuclide. Potential confounding by chemical exposure. Multiple myeloma results: small numbers, maybe a chance finding from multiple comparisons. Not possible to derive uranium-specific risks, because uranium doses not used
Boice et al. [B36]	Mortality in uranium miners and millers, Grants, New Mexico, 1979–2005: 1,735 underground uranium miners and 904 non-mining uranium millers. No measurements available on either radon or uranium exposure levels	Increased mortality in underground miners: lung cancer, non-malignant respiratory disease, liver cirrhosis. No significant excess among non-mining millers.Among uranium millers: Total cancer: SMR=0.89, n=65 Lung cancer: SMR=0.85, n=21 Cerebrovascular disease: SMR=1.06, n=14 Heart disease: SMR=0.84, n=73 Non-malignant respiratory disease: SMR=1.07, n=25 No suggestive excesses of kidney cancer, liver cancer or lymphoma, but small numbers	One of few studies of uranium millers. Study suggests uranium exposure effects are small or absent but not possible to derive uranium-specific risks, because uranium doses not used
Dupree-Ellis et al. [D33]	Mortality (1942–1993) investigated among 2,514 white male workers at Mallinckrodt (USA) uranium processing plant. Mean cumulative total dose, 47.8 mSv. For ~11 years plant also processed pitchblende, which increased external radiation exposure	All cancer: SMR=1.05 (95% CI: 0.93, 1.07). Some evidence of excess kidney cancer (ERR per Sv=10.5, 90% CI: 0.6, 57; n=10) in relation to external radiation exposure	Only total dose analysed, mainly external radiation. Not possible to derive uranium-specific risks, because uranium doses not used
Kreuzer et al. [K16]	Circulatory system disease (CSD) mortality (1946–2008, n=9,039 CSD deaths) in 58,982 male German Wismut uranium miners. External radiation estimated using a job exposure matrix	Circulatory disease: ERR per Sv for external gamma radiation: −0.13 for CSD, −0.03 for ischaemic heart disease, and 0.44 (95% CI: −0.16, 0.44) for cerebrovascular disease	Analysis for external radiation exposure only. Not possible to derive uranium-specific risks, because uranium doses not used

Study references	*Summary of study*	*Summary of findings relating to uranium*	*Relevance for this report*
Lane et al. [L8]	17,660 Canadian Eldorado uranium workers (Beaverlodge and Port Radium miners, Port Hope uranium refinery/processing). Radon decay product exposure, mortality (1950–1999) and cancer incidence (1969–1999)	Significant associations of radon decay product exposure and lung cancer mortality (n=618) in each subcohort. No associations for any other cancers. No estimates of LLR risk	Analysis for radon decay products only. Not possible to derive uranium-specific risks, because uranium doses not used
McGeoghegan and Binks [M27]	Mortality and cancer incidence at UK Springfields uranium production plant, 1946–1995. Main activities, uranium fuel fabrication and UF_6 production. 13,960 radiation workers	No measurements of internal exposure; all analyses for external radiation exposure	No analyses of internal exposure. Not possible to derive uranium-specific risks, because uranium doses not used
McGeoghegan and Binks [M26]	Mortality and cancer incidence studied at UK Capenhurst plant, 1946–1995. Main activities, uranium enrichment for military or power plant purposes. 12,540 employees	No measurements of internal exposure; all analyses for external radiation exposure	No analyses of internal exposure. Not possible to derive uranium-specific risks, because uranium doses not used
McGeoghegan et al. [M30]	407 workers involved in 1957 Windscale uranium pile fire. Mortality and cancer incidence 1957–2007. Estimated plutonium, but not uranium, doses	No measurements of internal exposure; only external radiation analyses	No analyses of internal exposure. Not possible to derive uranium-specific risks, because uranium doses not used
Pinkerton et al. [P21]	Mortality of 1,484 men employed in 7 uranium mills in Colorado Plateau, USA (1940–1998). Mortality (SMRs) examined by duration of employment and time since first employment	No individual estimates of radiation exposure were made	No data available on internal exposure. Not possible to derive uranium-specific risks, because uranium doses not used
Rooney et al. [R22]	Nested case-control study in five UKAEA facilities of incident and fatal prostate cancer and exposure to radionuclides. 136 prostate cancer cases diagnosed 1946–1986 and 404 matched controls. 28 (21%) prostate cancer cases and 46 (11%) controls had potential exposure to ^{3}H, ^{51}Cr, ^{59}Fe, ^{60}Co and/or ^{65}Zn	Prostate cancer: risk increased with duration and concentrations of exposure to the targeted radionuclides (possible exposure RR: 2.36, 95% CI: 1.26, 4.43; documented exposure RR: 5.32, 95% CI: 1.87, 17.2) Indicated prostate cancer not associated with uranium exposure; but uranium exposure was rare. Found 0 cases and 6 controls with documented uranium exposure (RR=0, 95% CI: 0, 2.55)	Negative association with uranium exposure (yes/no). Not possible to derive uranium-specific risks, because uranium doses not used
Vacquier et al. [V1]	French CEA-COGEMA uranium miners (1946–1990) followed up through 1999, mean 30.1 years. Radon exposure estimates from ambient monitoring and worker job, location and year. LLR exposure not estimated	Elevated SMRs for total cancer (SMR=1.19), lung cancer (SMR=1.43) and kidney cancer (SMR=2.00), but not leukaemia. Significant radon dose response for lung cancer, but not kidney cancer or leukaemia. No analyses with regard to LLR exposure	Not possible to derive uranium-specific risks, because uranium doses not used
Walsh et al. [W6]	Radiation dose and prostate cancer mortality examined in the 1970–1990 subset (55,435 miners) of German Wismut uranium mining cohort. Follow-up, 1970–2003, n=263 prostate cancer deaths. Only gamma dose analysed	External gamma dose response: ERR per Gy=−1.18 (95% CI: −2.4, 0.02)	Study analysed external dose and prostate cancer mortality. Not possible to derive uranium-specific risks, because uranium doses not used

Table A7. Studies of workers monitored for potential exposure to uranium, with occupational dose records, but uranium-specific doses not explicitly analysed

Study references	*Summary of study*	*Summary of findings relating to uranium*	*Relevance for this report*
Boice et al. and Ritz et al.[B38, R16]	46,970 employees, Rocketdyne, USA (1948–1999); 5 801 had radiation exposure, 2,232 monitored for internal radionuclides. Mortality follow-up 1948–2008 (mean 33.9 years). Activities: operating research nuclear reactors, fabricating nuclear fuel, disassembling and decontaminating reactor facilities, decladding spent nuclear fuel and storing nuclear material. Intakes of 14 radionuclides calculated for 16 organs using ICRP biokinetic models; >30,000 urinalyses. Most significant internal exposue was from enriched uranium, especially for lung and kidney. A few workers received high lung doses (~0.3 Sv) but 87% of workers had committed equivalent dose to all tissues well below 10 mSv	For those monitored for internal exposure, no SMR excesses seen for any cause: all cancers (except leukaemia); leukaemia; cancers of lung, kidney, stomach, liver, prostate, brain; heart disease and cerebrovascular disease Uranium doses, RR at 100 mSv: All cancer except leukaemia: 0.98 (95% CI: 0.82, 1.17, n=266) Lung cancer: 1.01 (CI: 0.89, 1.16, n=94) Non-CLL leukaemia: 1.06 (CI: 0.50, 2.23, n=10) Other trends for internal (mainly uranium) exposure: non-significant increasing trends, cancers of stomach, kidney, brain/CNS, lymphomas; Non-significant decreasing trends, cancers of colorectum, pancreas, prostate, bladder, and non-malignant respiratory disease	Sufficient data to estimate internal radionuclide exposure on basis of urinalyses. Uranium was largest contributor to internal dose but other radionuclides also present. Study limitations: relatively low career doses, incomplete information on smoking. Study does not suggest any strong uranium risk but has uncertainties regarding uranium doses and small numbers of deaths
Dufey et al. [D30]	Leukaemia nested case-control study in cohort of 58,987 German Wismut male uranium miners, 1946–2003; 128 leukaemia cases (40 CLL and 88 non-CLL) and unspecified number of controls. Mining performed 1946–1989. Cohort mean dose 48.8 mGy, of which external gamma contributed 40.9 mGy	Leukaemia: analyses for total dose to red bone marrow. For a 2-years lag, linear ERR per Gy was 1.39 (90% CI: −0.77, 3.56) for all leukaemia and 2.08 (−0.84, 4.99) for non-CLL. Suggestion of increased non-CLL only for the highest dose group: for 0.4, 5.0, 25.6 and ≥103.7 mGy RRs were 0.53, 0.89, 0.67 and 1.25 (90% CI: 0.69, 2.20), respectively	Strengths included large cohort, long and high quality follow-up. However, no assessment of LLR uranium exposure, so study uninformative regarding uranium effects
Dufey et al. [D31]	Liver cancer mortality (n=159) in cohort of 58,987 male German Wismut uranium miners, 1946–2003. Mining 1946–1989. Average liver dose, 47.9 mGy low-LET and 2.4 mGy high-LET irradiation; mean high-LET liver dose: 2.1 mGy from radon/progeny and 0.8 from LLR. Arsenic measurements available	Liver cancer: the analysis by high-LET dose categories did not reveal any statistically significant elevations in risk, and dose-response analysis, adjusting for low-LET dose, age and calendar years, yielded ERR per Gy=48.3 (95% CI: −32, 129). Examined confounding factors including arsenic exposure and alcoholism	Analysis adjusted for low-LET radiation exposure, but did not account for radon decay product exposure. Contribution of LLR to total absorbed liver dose was <2%, so study provides little information regarding uranium risk
Dupree et al. [D34]	995 white male employees (1943–1949) of Linde, USA uranium processing company followed up 1943–1979. Doses reconstructed from ambient monitoring data, surface contamination, urinalysis and film badges. Exposure mainly to uranium with low solubility. Job exposure was categorized as <10, 10–100 and >100 mSv/y of internal exposure (which was greater than external exposure levels)	Elevated SMRs found for laryngeal cancer (SMR=4.47, 95% CI: 1.4, 10.4, n=5), arteriosclerotic heart disease (SMR=1.19, CI: 1.01, 1.39, n=159) and non-malignant respiratory diseases (SMR=1.52, CI: 1.04, 2.14, n=32). No excess risk seen for lung, colorectal or lympho-haematopoietic malignancies. No analyses by uranium exposure levels	No quantitative analyses by uranium exposure levels, so uninformative regarding uranium risk. Given the exposure information developed, cohort has some potential to contribute to future uranium risk assessment

Study references	*Summary of study*	*Summary of findings relating to uranium*	*Relevance for this report*
Guseva Canu et al. [G31]	Cancer mortality (1968–2005) examined in 2,709 male workers at French AREVA NC Pierrelatte uranium enrichment and conversion plant. 15 former uranium miners excluded. Uranium assessments: individual dosimetry badges; faecal/urine bioassays and in vivo measurements performed but not available	All cancer: the SMR=0.70 (95% CI: 0.60, 0.81, n=193) Lymphoma and rectal cancer: non-significant increases in rectal cancer (SMR=1.48, n=10) and non-Hodgkin's lymphoma (SMR=1.32, n=8). Trend analyses by time first employment and length of employment not significant for all cancer, lung cancer, upper aero-digestive tract cancer, and lympho-haematopoitic malignancy	Mortality in relation to internal radiation dose not reported, so study uninformative regarding uranium risk
Kreuzer et al. [K15]	Stomach cancer mortality (1946–2003; n=592) in 58,677 male German Wismut uranium miners and exposure to external radiation, alpha radiation, fine dust with silica and arsenic. Mean estimated LLR exposure, 4.1 kBqh/m^3 (<0.05 mGy), was substantially correlated with arsenic exposure	Stomach cancer: for alpha irradiation, ERR per Gy=22.5 (95% CI: −27, 72) with statistical adjustment for other exposure variables. RR in highest alpha dose category (10–26 mGy) not significant: 1.59 (CI: 0.69, 2.49)	Not analysed for LLR exposure. Only <1% of the alpha dose to the stomach due to LLR, so uninformative regarding a uranium risk
Mohner et al. [M52]	Nested case-control study of leukaemia mortality (1953–1998) among ~360,000 male German Wismut uranium miners. 377 leukaemia deaths and 980 controls matched on age. Cumulative red bone marrow (RBM) doses from external radiation, radon decay products, LLR and occupational medical diagnostic radiation (including 17,578 X-ray examinations), using a detailed job exposure matrix. Mean cumulative LLR RBM dose estimated to be <0.05 mGy	Added analysis of medical X-ray exposure to occupational radiation sources. Analyses were conducted only for total occupational RBM radiation exposure, both internal and external and for medical X-rays. Case-control analyses for LLR already reported in [M50]	Report is uninformative for assessing uranium risk since analyses were of all radiation exposure combined
Polednak and Frome [P24]	18,869 white males worked at the Oak Ridge TEC uranium conversion and enrichment plant (operated 1943–1947) but not at the Y-12 plant which succeeded it. Workers in some departments (e.g. chemical dept.) exposed to high ambient uranium dust. In 1945 average levels of uranium in air in various departments ranged from 25 to 300 µg/m^3. Among 226 men with urine samples, 72% had >0.01 µg/ml and 33% >0.05. Mortality 1943–1977	Elevation in lung cancer (SMR=1.22, 95% CI: 1.10, 1.36) but not higher among those working in areas with more uranium dust or those with longer employment. Mortality not elevated for stomach cancer (SMR=0.73), kidney cancer (SMR=0.75), bone cancer (SMR=0.90) or leukaemia (SMR=0.92)	Individual measurements of uranium exposure levels available for only an undefined subsample of workers, so dose-response analyses not conducted. Smoking information not available

Study references	*Summary of study*	*Summary of findings relating to uranium*	*Relevance for this report*
Rage et al. [R4]	Lung cancer mortality (1956–1999) studied among 3,377 French uranium miners hired ≥1955 when LLR and gamma ray measurements became available. Among 2,745 with exposure to uranium, mean was 1.63 kBqh/m^3 (maximum 10.36). LLR contributed only 1.3% of total alpha-particle lung dose. Annual lung dose due to LLR significantly correlated with doses from low-LET radiation (r=0.49), radon gas (r=0.53), and radon decay products (r=0.50)	Lung cancer: significant risk lung cancer mortality associated with total absorbed lung dose (ERR per Gy=2.94, 95% CI: 0.80, 7.53, n=66) and the alpha-particle absorbed dose (ERR per Gy=4.48, CI: 1.27, 10.9). Assuming RBE=20 alpha-particles, ERR per Gy for total weighted lung dose was 0.22 (CI: 0.06, 0.53). LLR ERR was 5.0 (CI: 1.2, 12.3) per 10 mGy	Statistical analysis of LLR provided only weak information; since LLR were correlated with and a small percentage of total exposure the LLR risk estimate may be inaccurate. No information on smoking habits. Therefore study provides little information regarding uranium risk
Zablotska et al. [Z1]	Mortality (1950–1999) and cancer incidence (1969–1999) of Port Hope, Canada radium and uranium process workers. 2,472 (87% males) worked only with uranium. Gamma was predominant radiation exposure, so analyses were of gamma and radon decay products (RDP), not of LLR. Urinalysis for uranium begun in early 1960s; alpha counting of urine samples for workers exposed to enriched uranium conducted on a limited basis, so not used in dose assessment	No significant elevations in various cancer SMRs. No excess cancer incidence seen for a number of cancer types or all cancer. Dose-response analyses reported for RDP and external gamma. In uranium workers, lung cancer RDP risk estimate non-significantly elevated. Other malignancies and circulatory diseases: no significant dose related elevations in risk for either RDP or external exposure	Study of uranium workers was negative, other than a weak association of RDP exposure and lung cancer incidence (but not mortality). Had no LLR exposure estimates, so analyses of uranium effects could not be presented. Substantial uncertainties: limited or no exposure information for early workers, lack of smoking information. Study uninformative regarding uranium exposure risk

Table A8. Studies of workers monitored for potential exposure to uranium for whom uranium-specific doses have been used in analyses so that uranium risks can be explicitly examined

Abbreviations: LLR, long lived radionuclides; n.e., not estimable

Study references	*Summary of study*	*Summary of findings relating to uranium*	*Relevance for this report*
Carpenter et al. [C7]	Case-control study of brain/central nervous system (CNS) cancer deaths in workers (1943–1977) at 2 nuclear facilities at Oak Ridge (ORNL and TEC/Y-12): enrichment of ^{235}U and conversion to UF_4 (TEC, 1943–1947); fabrication and testing of components for nuclear weapons (Y-12); nuclear energy technology R&D (ORNL). 72 male and 17 female brain/CNS cancer deaths (1943–1979). 4 matched controls per case. Work locations/years rated by industrial hygienist for levels of 26 agents, including uranium compounds	CNS cancer: 63% of brain/CNS tumours were malignant glial tumours. Ever exposed to uranium, odds ratio (OR)=1.06 (95% CI: 0.5, 2.3, p=0.88) with no exposure lag, or 0.94 with a 10 years lag. Lagged levels of graded uranium exposure (grades 1, 2 and 3, with 0=no exposure as referent) had non-significant ORs of 0.88, 1.01 and 0.70, respectively. Analysis by duration of heavier uranium exposure (grades 2–3, 10 years lag) showed: OR=0.86 for 1–3 years; 0.79, 3–10 years; 0.99, 10–20 years; 1.63, >20 years (n=3), not significant	Only semi-quantitative imputation of amount of exposure. No elevated risk was apparent, but the reliability of dose categories unclear. Limited information regarding uranium risk for brain/CNS tumours
Chan et al. (and supplement) [C17]	Mortality among 6,759 workers at Paducah Gaseous Diffusion Plant, USA studied for 1952–2003. Workers had potential exposure to external and internal radiation, uranium, several other metals, trichloroethylene and other chemicals. Urinalyses of uranium used to characterize the cumulative dose of internally deposited radionuclides as µg.years	RRs for different uranium exposure quartiles compared to exposure quartile (<21 µg.years) are provided in table 15 (lung cancer); table 17 (leukaemia and non-Hodgkin's lymphoma); table 18 (pancreatic cancer); table 20 (brain/CNS cancer)	Provides grouped quantitative information about the health effects of uranium exposure, though LLR linear dose-response risk coefficients were not given. Possible confounding by chemicals and smoking. Provides semi-quantitative information regarding uranium risk for several cancer sites
Checkoway et al. [C20]	Mortality (1947–1979) investigated among 6,781 white male workers at Y-12 uranium fabrication plant (Oak Ridge, USA). 3,490 monitored for internal exposure. Internal dosimetry: urine analyses begun in 1950, fully implemented by 1953, and in vivo measurements added in 1961. Internal lung doses calculated using metabolic models. For monitored workers, mean lung dose 82.1 mSv. Mean external dose, 9.6 mSv. Other exposure: beryllium, solvents, machine oils, mercury, lead. 45 lung cancer deaths in those monitored for uranium exposure	Lung cancer: (n=45) Analysis with 10-years dose lag for alpha irradiation, compared to 0–<10 mSv group, 0–49 mSv, RR=0.93 (95% CI: 0.41, 2.12) 50–99, RR=0.66 (CI: 0.23, 1.90) ≥100, RR=1.12 (CI: 0.47, 2.65, n=11) Brain/CNS cancer: (n=14) with no lag, 10–49 mSv, RR=1.10 (0.19, 6.5) ≥50 mSv, RR=0.45 (0.06, 3.2) Other cancers: no bone cancers observed. Trend analyses for kidney cancer (n=6) or other a priori cancers not reported for uranium monitored cohort	Provides some information on lung cancer among those with measured uranium exposure; showed little apparent risk. Small numbers of lung and other cancers limit the quantitative estimates. Smoking information not available. Provides semi-quantitative information regarding uranium risk for lung and brain/CNS cancers

Study references	*Summary of study*	*Summary of findings relating to uranium*	*Relevance for this report*
Drubay et al. [D24]	A case-control study of circulatory system disease (CSD, n=442) mortality, particularly ischaemic heart disease (IHD, n=167) and cerebrovascular disease (CeVD, n=105), and 237 matched controls, nested among 5,086 French CEA-COGEMA uranium miners who were first employed after 1955, followed up through 2007, mean 35.4 years. Individual exposure estimated from ambient monitoring, 1959–1982 and dose reconstruction for 1956–1958. Since 1983, individual LLR exposure estimated with film dosimeters. Mean cumulative LLR was 1.2 kBqh/m^3 (max=7.6)	Circulatory disease: statistically significant association of radon exposure with both CSD (hazard ratio (HR)=1.11/100 WLM) and CeVD (HR=1.25/100 WLM) risk. Records contained information on a number of medical CSD risk factors for a subset of cases and controls. After adjusting for radon and external gamma exposure and for empirically the main medical risk factors, found LLR HRs per kBqh/m^3 of: CSD: 1.13 (95% CI: 0.97, 1.31, n=76) IHD: 0.94 (CI: 0.73, 1.20, n=26) CeVD: 1.17 (CI: 0.90, 1.53, n=16) LLR risks in entire nested case-control sample, but without being able to adjust for medical risk factors, nearly identical	Had a substantial set of individual measurements of LLR exposure. After adjusting for radon and external radiation, detected no significant LLR risk for CSD, IHD or CeVD. Confounding by medical CSD risk factors proved to be small. Uncertainties: exposure prior to 1983 estimated from ambient measurements or with no measurements may have had appreciable measurement error. Relevant for uranium risk assessment of CSD
Drubay et al. [D23]	Kidney cancer mortality in 3,377 French uranium miners 1956–2007, and 58,986 German uranium miners 1946–2007. For respective French and German cohorts, median durations of follow-up were 30.0 and 34.8 years; respective median kidney doses were 26.7 mSv (range 0, 498) and 34.4 mSv (range 0, 2 905)	Kidney cancer: SMRs were 1.49 (95% CI: 0.73, 2.67, n=11) for French cohort and 0.91 (CI: 0.77, 1.06, n=174) for German cohort. A 10-years lagged LLR dose-response analysis showed hazard ratio (HR) per kBqh/m^3 with 10-years lagged cumulative dose of 0.89 (CI: 0.55, 1.42) for the French and 1.009 (CI: 0.991, 1.027) for the German cohort	Lack of association with estimated LLR exposure suggests kidney cancer effect is likely small. Uncertainties: no information about smoking; French cohort was small; workers also had radon and external gamma exposure
Dupree et al. [D35]	Nested case-control study of lung cancer mortality (787 cases with 787 matched controls) in cohorts at 4 USA uranium processing facilites: TEC (operated 1943–1947 only) and Y-12 (1947–1982), Mallinckrodt (MCW, 1942–1966) and Fernald (FMPC, 1947–1982). Maximum follow-up period, 1943–1983. Primary radiation hazard was from airborne dust of mainly insoluble natural uranium compounds. For FMPC, MCW and TEC, ambient uranium monitoring to estimate internal radiation doses. Y-12 also had whole body counting and urinalysis. Conversion to doses assumed Type S uranium exposure. Smoking status available for 48% of cases and 39% of controls	Lung cancer: analysis of internal radiation (primarily from ambient uranium), using 10-years lagged dose with <0.5 mGy as baseline, showed no increased risk for workers exposed below 250 mGy. Lung cancer odds ratios (ORs) for 0.5, 2.5, 5, 25, 50, >250 mGy were 1.03, 0.57, 0.85, 0.82, 0.64 and 2.05 (95% CI: 0.20, 21), respectively for LLR. However, for the 166 case-control pairs with smoking data, no elevation in risk (odds ratio of 0.36 in the highest internal dose group)	Analysis had large number of lung cancer deaths, a fraction had urinalyses and/or whole body counting in addition to ambient monitoring data. Suggests that effect of uranium exposure must be small. Estimate of ERR per Gy not reported, but the grouped dose data do not suggest a statistically significant elevated lung cancer risk. Limitations: uncertain dose estimates for early workers, concomitant exposure to radon and external radiation, and limited smoking information. Provides semi-quantitative information regarding uranium risk for lung cancer

Study references	*Summary of study*	*Summary of findings relating to uranium*	*Relevance for this report*
Guseva Canu et al. [G31]	Lung cancer mortality in 2,709 workers at the French AREVA NC Pierrelatte uranium reprocessing plant during 1960–2005. The plant enriched uranium via gaseous diffusion caused uranium chemical conversion. Uranium was only radioactive material used at the plant. Semi-quantitative JEM to characterize uranium exposure (duration and intensity specific for each job and calendar year, on a 4 point ordinal scale). Smoking data on 6% of cohort	Lung cancer: (n=48) for durations of exposure >1 year to Type F, M and S uranium compounds found hazard ratios (HRs) of 1.05 (95% CI: 0.43, 2.52), 2.61 (0.87, 7.8), 2.58 (0.76, 8.8), respectively. For duration of exposure as a continuous variable, HRs of 1.01 (0.96, 1.01), 1.07 (1.01, 1.13) and 1.07 (1.01, 1.14) per year exposure, respectively	Suggestions of elevated lung cancer risk after exposure to slowly soluble (Types M and S) uranium compounds. However, substantial uncertainties: small number of lung cancer cases, only an ordinal scale of exposure intensity, limited smoking information, no individualized information on chemical exposure. Provides semi-quantitative information on uranium risk for lung cancer, with analyses by uranium solubility, but uncertainty due to small numbers
Guseva Canu et al. [G32]	Quantified uranium exposure using a job exposure matrix for 2,897 workers at French AREVA NC Pierrelatte uranium reprocessing plant. Classified exposure by natural vs. reprocessed uranium, and by solubility Types F, M and S. To model cumulative exposure for individuals, estimated duration and intensity of exposure to Types F, M and S	Lung cancer: (n=53) For natural uranium exposure, no significant associations for Type F, M or S. For reprocessed uranium, significant hazard ratios (HRs) in the highest cumulative exposure group of 4.35 (95% CI: 1.25, 15) for Type M and 10.5 (CI: 2.3, 48) for Type S. Dose-response analysis for reprocessed uranium exposure duration gave HRs of 1.13 (1.03, 1.25) and 1.13 (1.01, 1.25) for Types M and S, respectively. Analysis in subgroup of 345 workers with smoking information suggested no confounding by smoking Lympho-haematopoietic malignancies: (n=21) Found association with insoluble reprocessed uranium, but on the basis of only 3 exposed cases	This exploration of chemical types and radioactivity level of various forms of uranium suggests that natural uranium has little or no lung carcinogenic effect. However, the less soluble forms of reprocessed uranium dust, with their greater radioactivity and relatively long residence time, may induce lung cancer Limitations: study size was small. Only limited smoking data available. Results require confirmation in larger independent study
Guseva Canu et al. [G33]	Mortality from ischaemic heart disease (IHD, n=48), cerebrovascular disease (CeVD, n=31) and total circulatory system diseases (CSD, n=111) after chronic exposure to uranium among 2,897 workers at the French AREVA NC Pierrelatte uranium processing plant (1960–2006). Cumulative exposure to various uranium compounds was classified by isotopic composition and solubility type and quantified for individual job histories via a job-exposure matrix (natural vs. reprocessed uranium (RPU), and absorption Types F, M and S)	Circulatory disease: CSD mortality was increased among workers exposed to Type S RPU (HR=2.13, 95% CI: 0.96, 4.70) and Type S natural uranium (HR=1.73, CI: 1.11, 2.69). Additional information on risk by duration and intensity of exposure for CSD, IHD and CeVD is given in the text of table 20 For the subset of workers with available smoking data they found nominally higher CSD HRs for RPU Type M and S exposure among smokers than non-smokers, but numbers of cases were small	Job exposure matrix was carefully done, but provides only an approximate quantitation of uranium exposure. Concerns with study are: small study size, limited smoking data. Possible confounding: heat and trichloroethylene exposure were correlated with uranium exposure. The analyses of Types M and S RPU exposure did not adjust for the common exposure to Type F and natural uranium. Provides semi-quantitative information regarding uranium risk for CSD, including analyses by uranium solubility and isotopic composition, but with uncertainty due to small numbers

Study references	*Summary of study*	*Summary of findings relating to uranium*	*Relevance for this report*
Kreuzer et al. [K14]	Circulatory system disease (CSD) mortality (1946–1998), German Wismut male uranium miner cohort in relation to external radiation, radon and LLR exposure. Exposure estimated via a job exposure matrix JEM for each radiation type,1946–1989. 5,417 deaths from CSD (1946–1998), including 3,719 from heart disease and 1,297 from cerebrovascular disease. Mean LLR exposure, 3.5 kBqh/m^3 (maximum 132)	Circulatory disease: analyses for cumulative LLR exposure lagged by 5 years. The LLR risk estimates (ERR per 100 kBqh/m^3) were CSD: −0.2 (95% CI: −0.5, 0.06) Heart disease: −0.3 (CI: −0.6, 0.02) Cerebrovascular disease: −0.05 (CI: −0.5, 0.6) In no case did the highest dose category show significantly elevated risk. Ischaemic heart disease (n=2,690) also did not show a statistically significant elevation	The largest systematically defined cohort of uranium workers available. Uncertainties: no confirmation of JEM by urinalyses, correlation of LLR exposure with external radiation and radon exposure not accounted for, lack of dosimetric models to estimate LLR exposure of the heart and major arteries
Kreuzer et al. [K17]	Mortality from cancer of the extra-thoracic airways among 58,690 male German Wismut uranium miners (1946–2008) in relation to radon and cumulative LLR exposure. LLR exposure estimates derived by a job exposure matrix based on ambient measurements as described in Kreuzer et al. [K14]	Cancer of extra-thoracic airways (n=234): non-significant increase with radon exposure: ERR/100WLM=0.036, 95% CI: −0.009, 0.08 No increase with LLR exposure: ERR per 100 kBqh/m^3= −0.17, 95% CI: −2.50, 2.16 (adjusted for radon exposure)	Estimate of risk for uranium exposure had potential confounding by external radiation levels, arsenic and silica dust exposure and smoking habit. Quantitative risk estimate is relevant for uranium risk assessment: suggests little risk for extra-thoracic airways
Kreuzer et al. [K18]	Mortality in 4,054 male German uranium millers (1946–2008) who had never worked as uranium miners, so radon exposure was low, mean 8 WLM. Estimated exposure to radon, external gamma radiation, LLR and silica. Exposure estimates derived via a job exposure matrix of intensity (from ambient monitoring) by location, job, calendar year. Mean LLR: 3.9 kBqh/m^3. Preliminary organ dose calculations for alpha-emitting LLR averaged 3 mGy for lung, and 1 mGy for liver and red bone marrow	All cancer: LRR ERR per 100 kBqh/m^3 = −0.43 (95% CI: −1.31, 0.44, n=457), adjusted for radon exposure Lung cancer: LRR ERR=−0.61 (CI: −1.42, 1.9, n=159), (not adjusted for radon) Additional LLR risk coefficients given in text of table 16 (lympho-haematopoietic), table 17 (colon and rectal), table 18 (kidney and prostate), table 20 (circulatory)	Well conducted study, suggesting little/no association of uranium exposure with various health outcomes. Study size was small and no smoking information available. Quantitative risk estimates are relevant for uranium risk assessment
Mohner et al. [M50]	Nested case-control study of leukaemia mortality (1953–1989) among ~360,000 German Wismut male uranium miners: 377 leukaemia deaths and 980 controls matched on age. Job exposure matrix JEM by location, job and year used to estimate red bone marrow (RBM) exposure. JEM for radon and decay products (RDP), external radiation and LLR exposure estimates for >500 different workplaces, 750 job titles, 44 calendar years. Mean cumulative RBM dose was 23.6 mGy; only 2% from inhalation of LLR	Leukaemia: non-chronic lymphocytic leukaemia (non-CLL) risk not associated with RDP, but showed suggestive association with LLR exposure. ERR per 100 kBqh/m^3 for LLR was 1.04 (90% CI: −0.64, 2.73, n=377) for all leukaemia, 0.76 (CI: −1.26, 2.78, n=218) for non-CLL and 1.35 (CI: −1.54, 4.24, n=159) for CLL. Suggestion that the highest/longest LRR doses may increase risk: for ≥20 kBqh/m^3, (OR=1.26, 90% CI: 0.71, 2.22) for non-CLL. For acute myelogenous leukaemia, the LRR ERR per 100 kBqh/m^3 was 0.83 (CI: −1.9, 3.6)	Provides evidence that LLR exposure has little association with leukaemia risk. Limitations: prior to 1955 little data on exposure levels so dose uncertainties. Mortality may have been underascertained because inadequate identifiers in early years limited mortality linkage. Underlying cohort and numbers in it rather loosely defined, though it is the largest uranium worker cohort. Quantitative risk estimates are relevant for uranium risk assessment

Study references	*Summary of study*	*Summary of findings relating to uranium*	*Relevance for this report*
Mohner et al. [M51]	Nested case-control study of laryngeal cancer among ~360,000 German Wismut male uranium miners ever employed, 1950–1989. Tumour registry follow-up, 1961–1989. Two matched controls per case. Crude information on smoking habits available for many workers and anecdotal information on alcohol consumption from medical records. Included 554 laryngeal cancer cases and 929 controls	Laryngeal cancer: elevated risk in highest cumulative LLR exposure category (≥10 kBqh/m^3), OR=1.63 (95% CI: 1.03, 2.59, n=56), adjusted for smoking and alcohol intake. For continuous LLR cumulative exposure: ERR=0.098 (CI: –0.11, 0.31) per 10 kBqh/m^3, unadjusted, or ERR=0.156 (CI: –0.11, 0.41) adjusted for smoking and alcohol intake	The same limitations for this study as for Mohner et al. [M50]. Follow-up successful for only 72.8% of potential controls. Quantitative risk estimate for laryngeal cancer is relevant for uranium risk assessment
Rage et al. [R5]	5,086 uranium miners employed by CEA-COGEMA in France; followed up 1946–2007 (mean 32.8 years). Cohort included 3,377 miners first employed after 1955, for whom radon, LLR and external γ-ray exposure was recorded. Assessment of LLR exposure based on ambient measurements 1959–1982 and individual measurements thereafter. Doses retrospectively reconstructed for the period 1956–1958 [R4]. Post-1955 workers had mean of 1.64 kBqh/m^3 of LLR (range 0.01–10.4)	Internal LLR dose-response analyses were conducted, doses lagged 5 years. LRR results expressed as ERR/kBqh/m^3: All cancer, 0.022 (95% CI: –0.049, 0.12, n=315); Lung, 0.32 (0.09, 0.73, n=94); All cancers except lung, –0.065 (n.e. 0.019, n=221); Other LLR risk coefficients given in text of table 15 (respiratory), 19 (kidney), 20 (brain/CNS) and 21 (circulatory). In summary, only lung cancer showed a significant positive association with LLR exposure	LLR exposure related to various mortality end points. Limitations: LLR correlated with and a small percentage of total radiation exposure; smoking information unavailable; lung cancer analyses did not adjust for silica exposure. Quantitative risk estimates are relevant for uranium risk assessment
Richardson and Wing [R12]	Nested case-control study of lung cancer among 3,864 Y-12 (Oak Ridge, USA) workers hired 1947–1974. Y-12 was a nuclear material fabrication plant. Internal exposure primarily LLR from ambient uranium dust. Individual monitoring for external radiation exposure began in 1948 and became plant-wide in 1961. Urinalysis monitoring increased in coverage through the 1950s and in vivo monitoring begun in 1961. Mean external lung dose (10.1 mSv) was fourfold lower than mean cumulative internal dose (44.7 mSv). Other exposure: beryllium, solvents, machine oils, mercury, lead	Nested case-control analyses were conducted, with matched controls. Exposure lagged by 5 years Lung cancer: LLR dose-response negative (ERR per 100 mSv=–0.077, 90% CI: –0.23, 0.07) Smoking-related diseases other than lung cancer: LRR (ERR per 100 mSv=(–0.089) was negative, as was non-malignant respiratory disease (–0.085), but with wide confidence intervals	Provides evidence that uranium risk for lung cancer is likely small. Strength: measured exposure (both urine assays and in vivo monitoring) and the fact that radon exposure did not overshadow the LLR exposure of the lung. LLR exposure had substantial uncertainties, in part because 58% of exposure person-years had imputed rather than measured doses. Limitations: dose uncertainties, inadequate information on smoking and workplace chemicals, statistical power limited. Quantitative risk estimate for lung cancer is relevant for uranium risk assessment

Study references	*Summary of study*	*Summary of findings relating to uranium*	*Relevance for this report*
Silver et al. [S19] (Prior reports: [D33, R14, R15])	Cohort of 6,409 uranium workers at Fernald (USA) employed (1951–1985), and followed through 2004 (mean follow-up 37 years). Used urine uranium concentration data (>250,000 urine samples) from 1952 forward to estimate exposure to internally deposited uranium compounds. Mean cumulative doses to the lung for hourly and salaried workers were 1,552 μGy and 388 μGy for LLR, respectively. Mean LLR cumulative organ dose ranged from 1.1 mGy (lung) to 6.7 mGy (pancreas)	Analyses took into account pay code, birth year, trichloroethylene exposure, radon and external radiation. Overall: hourly males showed excess lung cancer (SMR=1.25, 95% CI: 1.09, 1.42, n=297). LRR ERRs calculated for Caucasian males per organ-specific 100 μGy: Intestinal cancer (small intestine and colon, not rectum): had a significant elevation in the highest dose group (>36 μGy, ERR=1.7, CI: 0.17, 5.7) and a significant dose response (ERR 100 per μGy=1.5, CI: 0.12, 4.1, n=48). Other dose-response estimates at 100 μGy for internal doses were null. Additional LLR risk coefficients given in text of table 15 (lung, respiratory), table 16 (leukaemia, lymphoma), table 17 (stomach, pancreas), table 18 (kidney)	This study has longer follow-up and better exposure assessment than previous ones. Uranium internal doses estimated for several different organs and linear ERR estimates adjusted for other radiation exposure. Sole positive finding related to intestinal cancer, which is not a very high a priori suspect, so requires confirmation. Limitations: no smoking data, limited data on exposure to chemicals and other hazardous substances, limited statistical power. Quantitative risk estimates are relevant for uranium risk assessment
Tomasek and Malatova [T13]	9,973 Czech uranium miners studied for leukaemia and non-Hodgkin's lymphoma risk. Two cohorts: S, 4,348 exposed 1948–1963; N, 5,625 exposed 1968–1986. Though had limited exposure measurements, derived location-job-year estimates of dose rates for hewers and then proportionately scaled for other jobs to develop a job exposure matrix JEM. Estimated 52–64% of the red bone marrow (RBM) dose was from LLR. Mean LLR RBM dose of 160 mSv for cohort S and 37 mSv for cohort N	Leukaemia: using 2 years dose lag, for 1–19 years since 1st exposure leukaemia SMR=1.0 (95% CI: 0.4, 2.1, n=7). For >19 years since 1st exposure SMR=1.8 (CI: 1.2, 2.7, n=23). For total follow-up period, SMR=1.5 (CI: 1.1, 2.2, n=30, mean RBM LLR dose 145 mSv). Due to small numbers, did not separate out non-CLL leukaemias. Leukaemia risk slope for total RBM dose (external, radon progeny and LLR), ERR per Sv=2.5 (90% CI: 0.3, 9.3) Non-Hodgkin's lymphoma (NHL): dose response not significant (p=0.16), though a nominal overall excess (SMR=1.5, CI: 0.9, 2.2)	Dose uncertainties were probably large, especially for earlier years (that contributed the highest exposure) and the number of malignancies was small. Analyses of LLR exposure were by average SMRs and not dose responses. Study suggestive of leukaemia risk from uranium exposure, but study limitations weaken the conclusions
Vacquier et al. [V2]	French cohort of 3,377 uranium miners first employed 1955–1990 when exposure to external radiation, radon and uranium dust (LLR) could be estimated. 3,240 had internal exposure. Follow-up through 1999, a mean of 26.5 years; mean LLR exposure, 1,632 kBqh/m^3. LLR exposure estimates: reconstructed before 1959; ambient measurements 1959–1982; since 1983 personal film dosimeters. Since external radiation, LLR and radon exposure instances were correlated, determined which were associated with cancer risks	LLR exposure was correlated r=0.52 with cumulative radon exposure, 0.47 with external exposure. Combined cumulative radiation exposure showed significant dose response only for lung cancer. Linear ERR risk coefficients per (kBqh.m^{-3}) for LLR exposure, lagged 5 years: All cancer: 0.001 (95% CI: –0.08, 0.11); Lung cancer: 0.25 (CI: 0.02, 0.70); Brain/CNS cancer: 0.17 (CI: n.e., 2.0)	LLR dose-responses could not be calculated with adjustment for radon or external exposure. Substantial correlation of LLR with radon and gamma exposure, so LLR risk estimates not well defined but suggestive small association with lung cancer. Limitations: uncertainties in exposure assessments, correlated exposure, lack of smoking data. Quantitative risk estimates are relevant for uranium risk assessment

Study references	*Summary of study*	*Summary of findings relating to uranium*	*Relevance for this report*
Yiin et al. [Y3]	Nested case-control study of multiple myeloma among 47,941 workers at the K-25 Oak Ridge, USA gaseous diffusion uranium enrichment plant (operated 1945–1985). Five matched controls per case. Exposure to soluble and insoluble uranium compounds. Individual uranium dose estimates based on ambient measurements and urinalysis. Formed groups according to the strength of the dosimetry: grouping I, multiple urinanalyses and extensive ambient measurements; groupings II also included those with fewer measurements; grouping III, all cases and controls. External radiation doses and medical radiation exposure also compiled	Multiple myeloma: 98 multiple myeloma death cases and 490 controls. Analyses adjusted for birth cohort, external and medical irradiation, mercury, nickel and trichloroethylene exposure. For those with the best estimated uranium doses to the bone marrow (Group I), the odds ratio (OR) at 10 μGy was 1.04 (95% CI: 1.00, 1.09). For total case-control group (Group III), OR was identical: 1.04 (CI: 1.00, 1.09). Indicated a weak association of bone marrow dose from uranium with multiple myeloma risk	High quality study. Included detailed uranium exposure assessment and analyses adjusted for external and medical radiation doses and prevalent chemicals. Weak association found between uranium bone marrow dose and multiple myeloma risk; requires confirmation by other studies. Limitations: less measurement data were available for workers in the earlier days. Quantitative multiple myeloma risk estimate is relevant for uranium risk assessment
Zhivin et al. [Z10]	Studied 4,688 French gaseous diffusion uranium enrichment workers (AREVA NC, CEA and Eurodif) with exposure to mainly soluble uranium compounds (Type F). Used plant-specific job exposure matrices JEMs to estimate cumulative exposure. The AREVA NC job exposure matrices showed 64% sensitivity and 80% specificity in validation against bioassay data. Median follow-up, 30.2 years, 1968–2008. Had estimates of potential confounding exposure situations: trichloroethylene, heat, noise	From job exposure matrices, grouped workers into no, low, medium, high exposure for analysis. Analysed external radiation, and natural, enriched and DU. Analysed all cancer, lung cancer, lympho-haematopoietic malignancies, and circulatory diseases. Results by exposure group presented in text of table 15 (lung), table 16 (lympho-haematopoietic), table 20 (circulatory)	Study developed quantitative estimates of uranium exposure, but analysed only low, medium and high grouped uranium exposure. Valuable because it considered mainly highly soluble uranium and compared natural, enriched and depleted isotopic forms. Provides semi-quantitative information regarding uranium risk for CSD, including analyses of isotopic composition

Table A9. Studies of groups with potential military uranium exposure

Study references	*Summary of study*	*Summary of findings related to uranium*	*Relevance for this report*
Bogers et al. [B28]	Following lay-press reports of alleged excess leukaemia among Dutch Balkan veterans, study examined cancer incidence, comparing 18,175 Balkan-deployed military male personnel with 135,355 non-Balkan deployed military males and with general population rates. Maximum follow-up was for nearly 15 years. Some differences between the Balkan and non-Balkan cohorts' military status, e.g. conscripted soldiers (15% vs. 81%, respectively)	All cancer: total cancer incidence 17% lower among Balkan than non-Balkan personnel (hazard ratio (HR) 0.83, 95% CI: 0.69, 1.00) Miscellaneous cancers: rates of digestive, respiratory, urogenital and haematological cancers non-significantly lower in the Balkan vs. non-Balkan group Leukaemia: HR could not be calculated for leukaemia because of the small number of cases (Balkan n=5)	No information about exposure to DU available, so study non-informative about uranium effects
Hines et al. [H18]	37 US Gulf War I veterans who had inhalation exposure to (and sometimes retained fragments of) DU from friendly fire incidents were examined. Compared those with high vs. low body burdens of DU, as measured by urine assay. DU remaining in the body is 40% less radioactive but chemically similar to natural uranium. Low and high exposure groups similar in age, race, BMI and smoking	Non-malignant respiratory disease: no differences between low and high exposure groups for any of a list of pulmonary symptoms or for history of steroid prescriptions. No significant differences regarding DU exposure levels in pulmonary function parameters or chest CT findings	Study strengths: had clinical examinations, spirometric testing, symptom reporting, and smoking information. DU findings do not indicate any non-malignant pulmonary effects. Provided limited information regarding uranium effects due to small sample size and likelihood that exposure levels were low
Labar et al. [L3]	Ecological study to examine childhood haematological cancers in Croatian counties with DU (10 counties), chemical plant damage (2 counties) or "population mixing" (4 counties). Compared disease rates for children ages 0–14 before (1986–1990), during (1991–1995) or after (1996–1999) the Croatian war in those counties	Childhood haematological malignancies: in the 10 counties with DU exposure, no significant increases during or after the War were found for lymphatic leukaemia, myeloid leukaemia, Hodgkin's lymphoma, or non-Hodgkin's lymphoma	No evidence for an effect of DU on childhood haematological malignancies. Exposure very low, and ecological data are susceptible to various unidentified biases, so study provides no meaningful information on uranium risk
Macfarlane et al. [M2]	A 13 year follow-up was conducted of 51,753 UK veterans deployed in the Gulf War and 50,808 other veterans matched for age-group, sex, rank, service and level of fitness, who were not deployed to the Gulf. 57% responded to a questionnaire about deployment experiences and morbidity	7% of those with questionnaires responded they had received DU exposure, among whom there were 9 disease-related deaths. The DU exposed vs. unexposed yielded a RR=1.00 (95% CI: 0.99, 4.04) after adjustment for age, sex, smoking and alcohol intake	DU exposure was based on unverified self-reports and the risk estimate was for overall disease deaths, not a priori causes. The small number of deaths (n=9) among those reportedly exposed to DU is a very weak finding
McDiarmid et al. [M22]	US Gulf War veterans with DU exposure were followed up (1991–2005) for clinical and laboratory end points. On basis of repeated urine uranium measurements, 10 were designated as high DU exposure and 24 as low exposure. Exposure resulted from inhalation, wound contamination and/or embedded fragments (for ~30%)	The extensive clinical examination did not show any differences between the high and low exposed group. Other high/low exposure comparisons: no difference in urine retinol binding protein, a biomarker of renal proximal tubule function. No differences found on: other renal measures, a neurocognitive test battery, neuroendocrine parameters, semen parameters, or HPRT mutations. A borderline increase in chromosome aberrations in the high exposure group	Among the several dozen parameters measured, only chromosome aberrations showed a (suggestive) difference. The multiple comparisons and small sample size limited the statistical power and meaningfulness of the comparisons

Study references	*Summary of study*	*Summary of findings related to uranium*	*Relevance for this report*
McDiarmid et al. [M23]	35 US Gulf War veterans with DU exposure in 1991 were again evaluated in 2007 with numerous clinical and laboratory measures	Only two parameters showed marginal differences between the high- and low exposure groups: β_2 microglobulin (81.7 vs. 69 µg/g creatinine, respectively; p=0.11) and retinol binding protein (48.1 vs. 31 µg/g creatinine; p=0.07). No differences were seen in rates of chromosome aberrations or HPRT mutations	Among the several dozen parameters measured, only two showed a suggestive difference. The multiple comparisons and small sample size limited the statistical power and meaningfulness of the comparisons
McDiarmid et al. [M25]	37 US Gulf War veterans with DU exposure in 1991 were again evaluated 20 years after exposure (2011) for numerous clinical and laboratory end points. Report focused on acute renal toxicity and included three new sensitive markers of kidney tubular injury	No differences between high- and low-exposure groups for: haematology, clinical chemistries, neuroendocrine parameters, bone metabolism, neurocognitive function, immune function, pulmonary function or nodules. Regarding renal function and injury, no high vs. low exposure differences were found for 16 clinical indicators of renal function, 6 urine markers for kidney injury, or 4 urine measures of low molecular weight proteins, although a re-analysis using a different definition of high exposure showed elevations in two kidney injury markers	Two sensitive markers of kidney tubular injury suggested subtle renal injury, but this found only after the main categories of high vs. low exposure showed no differences. Multiple comparisons and small sample size limit the inferences that can be drawn from the study
Strand et al. [S42]	Cancer risk and all cause mortality studied among 6,076 Norwegian military UN peacekeepers in Kosovo, 1999–2011. No information available on DU exposure. Mean follow-up, 10.2 years; 4.4% women	69 cancer cases observed (SIR=1.04, 95% CI: 0.81, 1.33). Suggestion of elevation in melanoma (SIR=1.90, CI: 0.95, 3.4, n=11). No elevation in stomach, liver, lung, prostate, kidney, bladder, brain cancers or lympho-haematopoietic malignancies	With no data on DU exposure, study is uninformative regarding uranium risk

Table A10. Studies of general population groups with potential environmental exposure to uranium by inhalation

Study references	*Summary of study*	*Summary of findings related to uranium*	*Relevance for this report*
Boice et al. [B31]	Study evaluated cancer incidence (1993–1997) among residents near Apollo (began operations 1957) and Parks uranium-plutonium processing plants in Pennsylvania, USA. Study population included about 17,000 individuals in 8 nearby municipalities	All cancer: found 581 incident cancers when 574 were expected (SIR=1.01, 95% CI: 0.93, 1.10) A priori tumour sites: for tumour sites with potentially greater exposure they found: lung (SIR=0.88), kidney (SIR=1.05), non-Hodgkin's lymphoma (SIR=1.10), liver (SIR=0.61) and bone (2 observed, 1.19 expected), none of which were statistically significant elevations. Also thyroid and female breast cancer rates were not elevated, nor was leukaemia	Earlier investigation had obtained soil measurements of uranium, plutonium and other isotopes and air measurements of gamma radiation; all levels well below Nuclear Regulatory Commission release guidances. Those measurements too sparse to be used to directly assess uranium effects associated with exposure of individuals. Limited environmental measurements and negligibly low exposure levels mean study is not informative as to uranium effects
Boice et al. [B30]	People in two counties proximal to the Apollo and Parks, Pennsylvania, USA former uranium/plutonium material processing plants were concerned regarding possible elevated rates of cancer, especially childhood leukaemia. Study compared cancer mortality rates in those two counties (population ~443,000) with six other counties (population ~864,000) matched on age, race, urbanization and socioeconomic factors. Comparisons made before, during and after operations of the uranium-plutonium plants	All cancer: during 1950–1995, 39,287 cancer deaths occurred in the proximal counties and 77,382 in the control counties. Compared to control counties, RRs in proximal counties for all cancer deaths before (1950–1965), during (1965–1980) and after (1980–1995) were virtually identical—0.95, 0.95 and 0.98, respectively—indicating no effect of potential uranium/plutonium exposure A priori tumour sites: for childhood leukaemia (total n=119 proximal county cases and n=272 control cases) before, during, after RRs=1.02, 0.81, 0.57, respectively. Lung cancer (RR=0.85, 0.99, 0.95), bone (RR=0.96, 1.00, 1.01), liver (RR=0.98, 1.07, 1.01) and kidney (RR=1.00, 1.08, 1.02) not significantly elevated in the proximal counties	Strengths: the mortality ascertainment was high, sample size was large. Most likely uranium-related cancer types examined Weaknesses: no individual or even county-level estimates of uranium exposure levels. Proximal county areas were rather broad, further diluting possible exposure, though nearly all inhabitants lived within 20 miles of a processing plant Conclusion: because of low exposure levels and ecological nature of the study, does not adequately address the health risks of uranium
Boice et al. [B32]	Cancer mortality rates investigated in Karnes County, Texas, USA, a county with uranium mining and milling activities from 1959 to early 1990s, with 3 mills and >40 mines. No uranium enrichment activities. Karnes cancer mortality rates before, during, after that period (1950–2001) compared with four match control counties. 1,223 cancer deaths observed in Karnes County (1,392 expected) and 3,857 in control counties. Texas Department of Health monitored Karnes radiation levels, found no elevations in radioactive material in/near homes	All cancer: Karnes County RRs of 1.0 in 1950–1964 (before/beginning of mining-milling), 0.9 in 1965–1979 (early operations), 1.1 in 1980-1989 (later operations and latency period) and 1.0 in 1990–2001 (few/no operations) A priori tumour sites: for prime exposure periods (1965–1979 and 1980–1989), Karnes county RRs were 1.0, 1.2, respectively, for lung cancer, 0.8, 0.9 for kidney cancer, 1.0, 0.8 for liver cancer, and 1.3 (n=20) and 1.7 (n=17) for leukaemia. no RRs significantly elevated. Childhood cancer mortality 1965-2001, non-significant RR of 1.3 (n=8 cases)	Strengths: mortality ascertainment was high. A priori cancer types specifically examined Weaknesses: limited uranium exposure measurements available to use in analysis. Cancer mortality misdiagnoses, especially for liver cancer Relevance: because of low, unknown exposure levels and ecological nature of the study, does not adequately address the health risks of uranium

Study references	*Summary of study*	*Summary of findings related to uranium*	*Relevance for this report*
Boice et al. [B34]	Mortality evaluated during 1978–2004 for 1936–1984 residents of Uravan, Colorado USA, a uranium mill town. Mining and milling activities during mid-1930s to 1984. The mean follow-up time since first Uravan residence, 38.1 years	All cancer: no significant elevation in overall cancer mortality or cancers of lung, kidney, breast; leukaemia; non-malignant respiratory, renal or liver disease among females or the 622 uranium mill workers, but excess lung cancer found among underground uranium miners. Had no quantitative information on exposure levels of mill workers	Study uninformative regarding uranium effects because no uranium exposure data and has low statistical power
Boice et al. [B35]	Comparison of 1950–2000 mortality in Montrose County, Colorado, USA (Uravan and other mining/milling operations) with five comparison counties	All cancer: no difference in total cancer A priori tumour sites: montrose elevation of lung cancer in males (RR=1.19, 95% CI: 1.06, 1.33), thought to be due to underground miner radon exposure and heavy smoking. No excess of breast, kidney, bone, liver or childhood cancer, leukaemia, non-Hodgkin's lymphoma, renal disease or non-malignant respiratory disease	Since no information on who was exposed to uranium and exposure levels, study uninformative regarding uranium risk
Boice et al. [B37]	Cancer incidence (1982–2004) and mortality (1950–2004) in Grants, New Mexico, USA residents: Grants mining during early 1950s to 1990; milling operations 1958–1990	Lung cancer: found increased mortality from lung cancer among men (SMR=1.57, 95% CI: 1.21, 1.99) Stomach cancer: stomach cancer mortality among women was high (SMR=1.30, 95% CI: 1.03, 1.63), but elevated mainly in the early years before milling operations began	Lung cancer excess was likely due to miner radon exposure and smoking. Uranium exposed individuals not identified, so it is uninformative
Chen et al. [C24]	Ecological study of cancer incidence in Port Hope, Ontario, Canada residents, 1992–2007. In 1981–1982, air uranium concentrations averaged 0.02 μg m^{-3} leading to a committed effective dose of 0.16 mSv, but by 1988–1989 were reduced to 0.00105 μg m^{-3}. Larger doses received from gamma and radon exposure. Population ~16,500	Standardized incidence ratio (SIR) for leukaemia, 0.86 (95% CI: 0.60, 1.21), with no elevation of childhood leukaemia rate SIRs were <1.0 for a number of other cancer sites. A significant elevation of lung cancer incidence, perhaps related to smoking habits	Provides some information on average air uranium levels, but analyses were ecological and not specific for uranium exposure. Study useful insofar as it rules out large uranium effects
Report of the Consejo de Seguridad Nuclear [C37]	Ecological study of cancer mortality in municipalities near seven nuclear power plants and five fuel cycle facilities (chemical conversion of uranium concentrate) in Spain. Cancer mortality (1975–2003) of municipalities within 30 km of facilities compared to similar municipalities 50–100 km distant	With reconstructed external doses, reported increasing dose-response trends for kidney cancer around nuclear power plants and for lung and bone cancers around fuel cycle facilities, but had not estimates of uranium exposure	Report is uninformative regarding uranium exposure effects, as it is an ecological study and only estimated external radiation exposure
Lopez-Abente et al. [L46]	Examined solid cancer mortality (1975–1993) in 283 towns in Spain within 30 km of one of four nuclear power plants or four nuclear fuel facilities, compared to 275 towns 50–100 km away, matched on various sociodemographic variables	They concluded that lung cancer and kidney cancer mortality rates were higher in the 30 km area, but other types of cancer were not	Various inconsistencies in the results depending on how the analyses were performed. They chose analyses that showed positive effects. No information presented on uranium exposure levels, so study is uninformative regarding uranium risk

Study references	*Summary of study*	*Summary of findings related to uranium*	*Relevance for this report*
Lopez-Abente et al. [L45]	Examined lympho-haematopoieticmalignancies (LHMs) in 489 towns within 30 km of Spain's seven nuclear power plants and five nuclear fuel facilities ("exposed"), compared to 477 towns 50–100 km away ("unexposed"). Exposed towns reported 610 leukaemias, 198 lymphomas and 122 multiple myeloma deaths during 1975–1993	No excess LHM found in towns near nuclear power plants. Reported excess leukaemia mortality near two nuclear fuel facilities and excess myeloma mortality near one nuclear fuel facility. No exposed town showed excess leukaemia for the under age 25 group. Analyses of all nuclear fuel facilities combined did not yield statistically significant excess for any end point (leukaemia, leukaemia <25 years, myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma)	Selecting a few "significant" results from a large number of statistical tests is questionable. The results for all nuclear fuel facilities combined, or all nuclear power plants, do not indicate elevated risks for lympho-haematological malignancies
Pinney et al. [P22]	Examined prevalence ratios of diseases among 8,496 residing within 2 miles (3.2 km) from Fernald, USA uranium plant, or within 5 miles (8 km) and in groundwater runoff direction, or with well/cistern. Medical conditions obtained by questionnaire and screening examination. Prevalences were compared to NHIS/NHANES data (national standardized surveys)	Reported a number of elevated prevalences of kidney and bladder diseases/conditions compared to NHIS data, but screening questions or coding sometimes differed between the two datasets. Found no differences for diabetes, thyroid diseases or respiratory diseases. Several clinical laboratory variables showed small but significant differences between those within 2 miles or more distant, and a different set of variables were significant for those using wells/cisterns	Distance from the plant and/or possible exposure to plant runoff used as surrogates for uranium doses. Actual measured exposure levels very low. Since perceived residential risks from Fernald were current in the population, results based on self reports may have been biased. Inconsistencies among comparisons of laboratory findings create uncertainty in the interpretation

Table A11. Summary of literature review on health effects of human exposure to uranium through ingestion of surface or groundwater

Study	*Study design*	*Country*	*Effect*	*Effect measurement*	*Relevance for this report*
Mao et al. [M9]	Cross-sectional	Canada	Chemical toxicity of urinary system	Comparison of biomarker levels in urine (microalbuminuria) and serum (creatinine)	Positive association between uranium cumulative exposure index and albumin level
Zamora et al. [Z6]	Cross-sectional	Canada	Chemical toxicity of urinary system	Comparison of biomarker (glucose, creatinine, protein, beta2-microglobulin, alkaline phosphatase, γ-glutamyl transferase, lactate dehydrogenase, N-acetyl-β-D-glucosaminidase) levels	Alkaline phosphatase, beta2-microglobulin levels correlated with uranium level in water
Kurttio et al. [K26]	Cross-sectional	Finland	Chemical toxicity of urinary system	Comparison of biomarker (calcium, phosphate, glucose, albumin, creatinine, beta2-microglobulin) levels	Significantly increased calcium, fractional excretion No association between uranium exposure and other parameters
Kurttio et al. [K28]	Cross-sectional	Finland	Chemical toxicity of urinary system	Comparison of renal damage indicators (glucose, creatinine, alkaline phosphatase, γ-glutamyl transferase, lactate dehydrogenase, N-acetyl-β-D-glucosaminidase, calcium, phosphate, cystatin C, glutathione-S-transferase) in urine	No statistically significant association between uranium concentrations in urine and any of the renal damage indicators, except glucose excretion in urine and diastolic blood pressure

Study	*Study design*	*Country*	*Effect*	*Effect measurement*	*Relevance for this report*
Selden et al. [S8]	Cross-sectional	Sweden	Chemical toxicity of urinary system	Comparison of biomarker (albumin, beta2-microglobulin, protein HC, kappa and lambda chains, N-acetyl-β-D-glucosaminidase) levels in urine	Significant increase in urinary excretion of β-2 microglobuline, kappa and lambda chains, and HC protein with medium to high uranium concentrations in urine. Dose–response relationships observed after exclusion of subjects with diabetes
Kurttio et al. [K29]	Case-cohort	Finland	Urinary system as target of radio-toxicity	Comparison of risk of bladder cancer by uranium level and radiation dose	No excess of bladder cancer with increased level of uranium or radiation dose
Kurttio et al. [K27]	Cross-sectional	Finland	Bone as target of chemical toxicity	Correlation between uranium exposure and biomarkers associated with bone (osteocalcin, aminoterminal propeptide of type I procollagen, serum type I collagen carboxy-terminal telopeptide)	Marginal positive association of uranium concentrations in drinking water with serum type I collagen and carboxy-terminal telopeptide only in men (p=0.05) No significant association between uranium exposure and bone turnover indicators in women
Seiler [S7]	Ecological	USA	Lympho-haematopoietic system	Comparison of uranium concentration in wells used by case families and other wells	No significant difference between uranium concentrations in wells used by families of leukaemia cases (median=3.4 µg/L) and the uranium concentrations in other wells (1.6 µg/L) No differences in concentrations of gross α activity or of Rn (617 vs. 563 pCi/L)
Auvinen et al. [A32]	Case-cohort	Finland	Lympho-haematopoietic system	Comparison of risk of leukaemia according to uranium level	No excess of leukaemia according to uranium level of drinking water
Witmans et al. [W23]	Case-control	Canada	Lympho-haematopoietic system	Comparison of U_w and Th_w exposure between cases and controls	Cases had higher uranium concentrations in drinking water than controls (p=0.001) No significance difference in Th_w (p=0.22)
Auvinen et al. [A32]	Case-cohort	Finland	Digestive system	Stomach cancer risk according to uranium level	No excess of stomach cancer by uranium level

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