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The health hazards of depleted uranium munitions

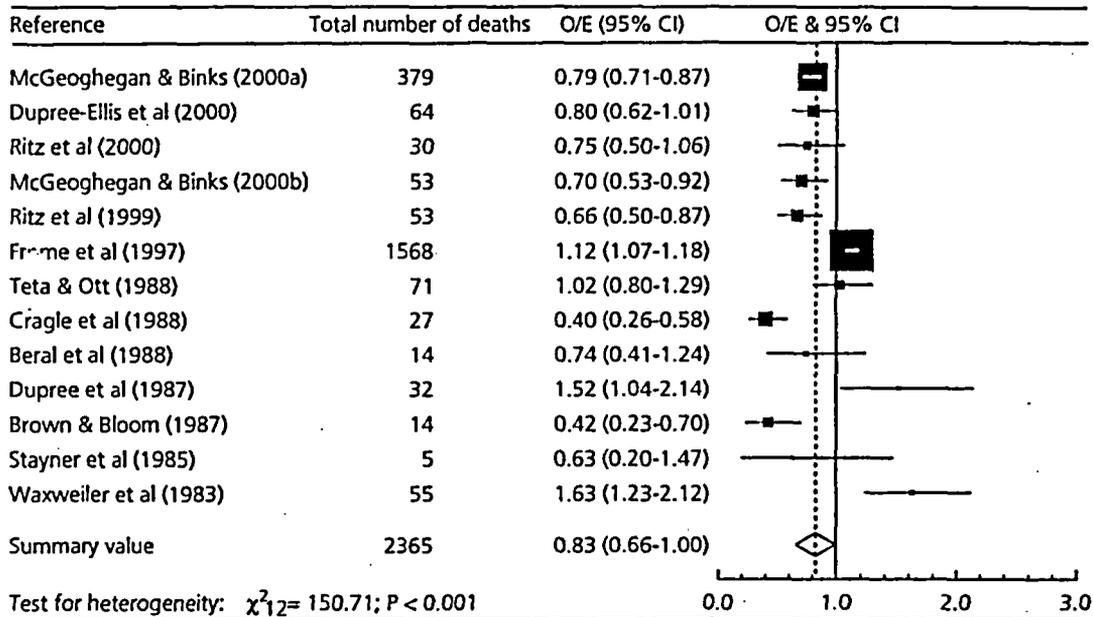
Part II

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Figure 1.6. Ratio of observed number of deaths from non-malignant respiratory disease in uranium workers compared to that expected in the general population.



1.7 Other non-malignant effects of uranium

1.7.1 Bone effects

Uranium accumulates in bone, which is thus considered a tissue at risk from the toxicity of large acute or chronic exposures to uranium. In the rat, both acute and chronic intakes cause a decrease in bone formation and may increase bone resorption (Ubios et al 1991). There is very little information on the effects of uranium on bone formation or strength in humans. It is therefore difficult to evaluate whether effects on bone are expected in those who have received large intakes of DU.

1.7.2 Immunological effects

In Part I of the report the radiological effects of exposure to DU were examined but these were restricted to effects on the incidence of cancer. At the public meeting it was suggested that we should examine whether radiation from internalised DU might have adverse effects on the immune system. Although Part II of the report focuses on the chemical toxicity of uranium, the possibility of radiological effects on the immune system is considered in Chapter 3.

1.7.3 Neurocognitive effects

Elevated uranium concentrations have been shown to be present in the hippocampus region of the brains (an area associated with memory and learning) of rats implanted with DU pellets and have been associated with slight alterations of the electrophysiology of the brain (Pellmar et al 1999b). A statistical relationship has been observed between uranium levels in the urine of US Gulf War veterans and poorer results in computerised tests that assessed performance efficiency, but effects on cognitive

ability were not observed (McDiarmid et al 2000). Possible effects of stress and anxiety resulting from their wounds and exposure to DU are difficult to rule out. Neurological and psychological problems are increased among Gulf War veterans (Cherry et al 2001a), but it is not possible to conclude whether this may be linked in any way to their exposure to DU or to any of the other potentially toxic exposures in the Gulf War.

1.7.4 Respiratory disease

Workers in the uranium industry and underground uranium miners have been chronically exposed to uranium dusts but there are few data on rates of non-fatal respiratory disease. Deaths from non-malignant respiratory diseases in uranium workers (excluding underground miners) are summarized in figure 1.6.

Overall the number of deaths observed in the combined studies was 17% fewer than the number expected from general population rates, although in three individual studies (Waxweiler et al 1983; Dupree et al 1987; Frome et al 1997) the numbers of deaths observed were significantly greater than the number expected from general population rates, by factors of 1.12, 1.52 and 1.63, respectively. Some studies therefore suggest a significant increase in mortality from non-malignant respiratory disease among uranium workers (NECIWG 2000), but in interpreting these results it must be remembered that mortality from many respiratory diseases (eg chronic bronchitis) is determined largely by smoking habits, and other toxic exposures may be present. However, the findings do rule out the possibility of large increases in respiratory deaths among uranium workers.

Occupational exposure to a number of metal dusts or fumes has been associated with several non-malignant lung diseases (Nemery 1990; Kelleher et al 2000). However, uranium is not one of the metals that have been clearly associated with these types of lung disease.

Scarring and thickening of lung tissue leading to shortness of breath and eventual cardiac failure has been observed in uranium miners but has been attributed to alpha-particles from highly radioactive radon progeny and possibly silicates (Archer et al 1998).

Pulmonary damage has also been observed in animals after long-term inhalation of some uranium compounds at concentrations above about 5 mg per cubic metre (Leach et al 1973; Spoor and Hursh 1973). Effects on the lung, including pneumonitis progressing to fibrosis and eventual death, have been observed in dogs following inhalation of aerosols of plutonium oxide, a highly radioactive alpha-emitter (Muggenburg et al 1988, 1999). These effects occurred at radiation doses to the lungs that were higher than, but of the same order of magnitude as, the lung doses from DU in the worst-case Level I intakes.

Some soldiers on the battlefield may receive inhalation intakes of DU oxides that are very substantially greater than the daily intakes that occur in chronically exposed uranium workers and the increased risks of lung cancer in such soldiers have been considered (see Part I). The nature of the inhalation intakes (particle size, presence of a significant ultrafine component, solubility, etc) are also likely to be different in the industrial setting (and in animal experiments) compared with the battlefield, which increases the difficulty in assessing the respiratory toxicity of inhaled DU. Acute respiratory effects would not be unexpected following the inhalation of large amounts of dense DU aerosols (for example, for any survivors in a tank struck by a DU penetrator or those working for protracted periods in contaminated vehicles).

It is unclear whether large inhalation intakes of DU would lead to sufficient alpha-particle irradiation of the lung to cause significant fibrosis, but the possibility perhaps exists for worst-case Level I or II intakes as the radiation doses are not very much lower than those at which pulmonary effects occur in dogs, and there is evidence that dogs may be about two-fold less sensitive to radiation-induced pulmonary damage than humans (Poulson et al 2000).

Long-term respiratory effects for soldiers who inhaled smaller amounts of DU from aerosols (most Level II and all Level III inhalation exposures) are considered unlikely.

1.7.5 Effects on reproductive health

Pellmar et al (1999a) reported significant levels of uranium in the testicles of rats implanted with DU

pellets. Uranium has been shown to be present in the semen of veterans retaining fragments of DU shrapnel and presumably would be present in the semen of soldiers heavily exposed to DU aerosols. This raises the possibility of adverse effects on the sperm from either the alpha-particles emanating from DU, chemical effects of uranium on the genetic material (Miller et al 1998a,b) or the chemical toxicity of uranium. Synergistic effects from the combination of both radiation damage and direct chemical damage to the genetic material are also possible (See Part I, Appendix 2).

Studies on the reproductive health of workers in the nuclear industry, and of survivors of the atomic bombs, show little evidence of decreased fertility, or of an increased incidence of miscarriages or birth defects (Otake et al 1990; Doyle et al 2000). For example, a large study of over 20,000 pregnancies in the partners of male radiation workers at the Atomic Weapons Establishment, the Atomic Energy Authority and British Nuclear Fuels who had been exposed to radiation prior to conception showed no increase in foetal deaths or malformations. The lack of effect was seen both for workers who were only monitored for external radiation and for those monitored for both internal and external radiation. A slight increase in early miscarriages and stillbirths was found in pregnancies involving women radiation workers exposed prior to conception, but its significance is unclear as there was little evidence that the effect increased with radiation dose (Doyle et al 2000).

Effects of uranium on reproductive health have been observed in male mice, although at very high intakes. Daily ingestion of large amounts of soluble uranium (between 10 and 80 mg uranium per kg per day; equivalent to 700 mg to 5.6 g per day for a 70 kg man) over nine weeks had no apparent effect on testicular function or sperm development, but there were some effects on the morphology of the hormone-producing cells in the testes at the highest exposure level. A decrease in male fertility was reported but this was not related to the level of uranium exposure and its significance is unclear (Llobet et al 1991).

In other studies, the offspring of male mice injected with plutonium-239 (a highly radioactive alpha-emitter) showed an increased predisposition to the induction of leukaemia by a chemical mutagen (Lord et al 1998), but the intake that would be required to produce the same dose to the testes of a 70 kg man using the much less radioactive DU would be far above that causing lethality due to the chemical toxicity of uranium. We are not aware of any animal studies that have looked for developmental abnormalities in the progeny of uranium-exposed males.

Uranium is known to cross the placenta (Sikov and Mahlum 1968; McClain et al 2001) and increased levels

of uranium in the mother will lead to increased levels in the foetus. The effects of exposure of pregnant mice to uranium have been studied by Domingo et al (1989a). Ingestion of 5 mg of soluble uranium per kg per day during pregnancy had no effect on sex ratios, mean litter size, body weight or body length of the newborn mice at birth or during the subsequent three weeks. Exposure of male mice to ingested soluble uranium for two months prior to mating with females that were also exposed prior to and during pregnancy resulted in some embryo lethality at intakes of 25 mg per kg body weight (Paternain et al 1989). Doses of 5 to 50 mg of soluble uranium per kg per day in food during pregnancy have been shown to reduce foetal body weight and body length, and to produce developmental defects including cleft palate and skeletal abnormalities (Domingo et al 1989b). These effects were particularly apparent at the 25 and 50 mg per kg dosages but some effects were apparent at 5 mg per kg. Developmental effects and malformations were also observed in mice born to mothers given daily subcutaneous injections that resulted in severe maternal toxic effects including death (Bosque et al 1993). The significance of these effects in mice is unclear as they occur at high intakes of soluble uranium that are equivalent to between 250 mg and 2.5 g per day for a 50 kg (eight stone) woman.

There are uncertainties in extrapolating from animal studies to humans and there is a possibility of effects on reproductive health for soldiers who have high levels of exposure to DU, and careful epidemiological studies are required. An important study of the reproductive health of male and female UK Gulf War veterans and the health of their children has been carried out by Dr Pat Doyle and colleagues, although the results of the study are not yet available. The study compares soldiers who served in the Gulf with a similar group of military personnel who were not deployed in the Gulf. The adverse endpoints being examined include infertility, foetal loss, low birth weight, congenital malformation and childhood illness. If there is a significant effect on reproductive health it will be difficult to establish whether this is due to DU or to any of the other potentially toxic exposures in the Gulf War.

There are reports in the media and elsewhere of increased rates of foetal death and malformations in children born in Iraq and Bosnia since the conflicts in these regions. These reports are of obvious concern but are very difficult to interpret as reliable data on the rates of foetal death and malformation prior to and following these conflicts are not available. Recently, the WHO has initiated studies to ascertain whether reproductive health in Iraq has declined since the Gulf War. If there have been increased rates of foetal death and malformation it will again be difficult to know whether this is due to DU as the population of Iraq has been subjected to multiple toxic exposures.

It should also be remembered that malnutrition can increase the incidence of malformations (eg the link between neural tube defects and folic acid deficiency is firmly established), and a deteriorating quality of food supplies and storage conditions can increase exposure to mycotoxins which are potent teratogens.

1.8 Conclusions

Uranium is a poisonous metal with its most toxic effects being exerted on the kidney. The levels of uranium in the human kidney that cause kidney damage, and the long-term effects of acute and chronic intakes of uranium are not well understood. Numerous studies with animals have been carried out but these show substantial differences in the lowest kidney uranium concentrations that result in adverse effects: In some studies with rabbits, chronic ingestion leading to kidney uranium concentrations as low as 0.02 µg per gram of kidney has observable effects on kidney morphology, whereas studies with rats indicate that concentrations as high as 0.7 µg per gram kidney have little effect. Current exposure limits for chronic ingestion of uranium for the general public have used the lowest chronic intakes that result in adverse effects on the kidneys of rabbits (Gilman et al 1998a) - ingestion of 50 µg soluble uranium per kg body mass per day - and have reduced this intake by a factor of 100 to take into account the uncertainties in extrapolating from rabbits to humans. Chronic ingestion of soluble uranium below this limit (0.5 µg per kg per day) should result in a kidney uranium concentration below 0.01 µg per gram of kidney. The tolerable daily intakes of uranium by inhalation are also expected to maintain the kidney uranium concentrations below this level.

The limited data on human exposures support the view that the level of 3 µg uranium per gram kidney proposed as a basis for occupational exposure limits is too high. Although the concentrations which produce toxic effects on the human kidney are poorly understood, most of the data are consistent with the view that adverse effects in humans can be detected at chronic intakes that result in kidney concentrations of about 0.1-0.5 µg uranium per gram, or acute intakes resulting in about 1 µg per gram, but the long-term effects (if any) of these elevated uranium levels are not clear.

The studies of human exposures that are of most relevance to the intakes of DU that occur on the battlefield are the small number of case reports that describe the effects of large acute intakes of uranium. These studies suggest that acute intakes predicted to result in peak concentrations of greater than 50 µg uranium per gram kidney are likely to result in very serious effects on the kidney that may be lethal in the absence of appropriate medical intervention. However,

this conclusion is based on a very few cases of large acute exposures. The kidney is a resilient organ and even individuals who have received these high intakes of uranium appear to recover kidney function, although some abnormalities may remain detectable for several years. The long-term effects of acute uranium poisoning in humans are not known but clearly could lead to an increased likelihood of kidney failure in later life.

Similarly, the long-term consequences of transient exposures to lower levels of uranium in the kidney are poorly understood. It is not possible to estimate with any confidence how long uranium concentrations that lead to slight biochemical signs of kidney dysfunction can be tolerated in humans, or how far above this threshold concentration exposures can be without long-term adverse effects on the kidney.

Epidemiological studies provide little evidence for increased rates of kidney disease in uranium workers, but the absence of reliable data on the levels of uranium in the kidney makes it difficult to estimate exposures to uranium that lead to no significant increase in mortality from kidney disease. There are few data on non-fatal kidney disease in uranium workers and conflicting evidence from post-mortem examination of the kidneys of uranium workers. Effects on kidney morphology have been observed in some studies but not in others. However, inhalation intakes of uranium particles in industrial settings are chronic and, even before the introduction of stringent occupational safety standards, the daily intakes were probably much lower than the acute intakes that could be received under worst-case assumptions by some soldiers. Furthermore, the forms of the inhaled particles in industrial settings will typically be different from those on the battlefield, and these differences might lead to significant differences in their ability to lead to adverse effects.

The central estimates of kidney uranium concentrations in all exposure scenarios on the battlefield are unlikely to cause acute kidney problems, although for Level I exposures, and to a lesser extent Level II inhalation exposures, the possibility of minor kidney damage exists. The worst-case Level I and Level II inhalation scenarios are expected to lead to very severe acute effects on the kidney. It is not clear whether such exposures to DU would occur on a battlefield, but the occurrence of acute kidney problems, requiring hospitalisation and critical care within a few days or weeks of DU exposure, would indicate that soldiers might have received intakes that lead to very high levels of kidney uranium. The toxic effects of DU from these worst-case scenarios should therefore be much easier to observe than the worst-case radiological effects, as the effects on the kidney are rapid and obvious, whereas the development of lung cancer will typically take several decades. It should be stressed that the worst-case estimates for kidney damage will not be the worst-

case for radiological effects. An individual with the worst-case estimate for lung cancer would therefore not have the worst-case risk of kidney damage and vice versa. However, for Level I inhalation exposures, the worst-case for radiological effects is still predicted to result in dangerously high peak kidney uranium concentration (about 50 µg per gram, compared with 400 µg per gram for worst-case chemical toxicity). For Level II inhalation exposures the peak kidney concentration would be much less under conditions which maximise radiation dose (about 3 µg per gram, compared with 96 µg per gram).

The fact that kidney function can be reduced by about two-thirds without any obvious symptoms, and the ability of the kidney to recover apparently normal function even after a large intake of uranium, has implications for the evaluation of the health of veterans. In the UK the Ministry of Defence Medical Assessment Programme for Gulf War Veterans recommends tests for uranium levels 'if the veteran has symptoms and signs that suggest such a test is clinically necessary'. This approach has no good scientific basis since several years after an exposure it is unlikely that any clinical signs (or perhaps even biochemical signs) of kidney dysfunction would be apparent, even in veterans who had been exposed to a large acute intake of DU. Any veterans who received intakes of DU that were substantial, but not large enough to cause acute symptoms of kidney damage, would not subsequently be identified so that their health (eg early signs of lung cancer) and kidney function could be followed. However, we should stress that, excepting Level I exposures, adverse effects on the kidney are not expected according to the central estimates of peak kidney uranium levels, although there might be significant kidney effects for some soldiers under the worst-case Level I and II assumptions. Long-term monitoring of kidney function using modern biochemical methods is recommended for any veterans who may have had substantial exposures to DU.

In animals, chronic exposure appears to lead to some tolerance to the nephrotoxic effects of uranium, which may explain the absence of signs of kidney dysfunction in veterans with retained DU shrapnel. The kidneys of animals with increased tolerance to uranium have been shown to have abnormalities (Leggett 1989) and the continuing surveillance of these veterans is required as kidney dysfunction in later life remains a possibility.

According to the central estimates, the long-term intakes of DU occurring after a conflict from resuspension of DU in soil are not expected to result in increased levels of kidney disease among returning civilians. Worst-case estimates of kidney uranium levels raise the possibility of some adverse effects on the kidney for inhalation intakes from resuspended DU.

Animal studies suggest that absorption of uranium from the gut of neonates might be higher than in older children or adults and that malnutrition could enhance the effect of uranium by increasing uptakes from the gastrointestinal tract to the blood. Malnutrition also can lead to ingestion of soil (geophagy), which if substantial could lead to significant intakes of uranium in DU-contaminated areas (Annexe C).

Short-term respiratory effects occurring soon after extremely large inhalation intakes of DU would not be surprising. Whether this would lead to any long-term respiratory effects is difficult to evaluate, but some fibrosis of the lung is perhaps possible if any soldiers received the worst-case Level I or II inhalation exposures.

Effects on immune function from the chemical effects of DU exposure or from internal radiation are considered unlikely. Exposure of the thoracic and extra-thoracic lymph nodes to alpha-radiation from retained particles of DU may lead to the killing of some immune cells traversing these lymph nodes but, in the absence of high doses to the red bone marrow, there is unlikely to

be any measurable increase in susceptibility to infection, or other significant adverse immune effects, from the intakes of DU that could occur on the battlefield (see Chapter 3). The possibility of very slight effects which could exacerbate any adverse effects on the immune system from other toxic exposures present in modern warfare cannot be discounted.

There is inadequate information about the effects of elevated levels of exposure to uranium on human reproductive health. There is no evidence that male radiation workers in the uranium industry have suffered adverse effects on their reproductive health. However, uranium is known to cross the placenta and, in mice, high intakes of uranium by the mother have been shown to have effects on the foetus but these occur at very high intakes of soluble uranium that are toxic to the mother. Epidemiological studies of the reproductive health of Gulf War veterans and of the Iraqi population are underway, but if any adverse effects are observed it will be difficult to link them to DU, or to other potentially toxic exposures on the battlefield or other possible reasons.

whether muscle and fat or bone marrow form major reservoirs for uranium in the human body and similarly whether uranium accumulates in the brain. An answer to the latter would be important in view of possible neurocognitive effects (see above). Similarly, uranium crosses the placenta and the effects of maternal exposure to DU on skeletal development in the foetus may also need to be considered.

5.7 Immunological effects

To the best of our knowledge there are no published studies of the effects of DU on immune function. However, it is unlikely that exposure to DU on the battlefield will lead to major changes in serum immunoglobulins, complement, or in B or T lymphocyte numbers or function (Personal communication, Professor Freda Stevenson). Kalinich et al (1998) have studied the effect of DU-uranyl chloride at concentrations up to 100 micromolar on the viability of rodent thymocytes, splenocytes and macrophages, and on human T-cell leukaemia and B-cell lymphoma cell lines, and a mouse macrophage cell line. Effects were only observed with macrophages that showed a dose-dependent loss of viability, appearing to undergo apoptosis, and had a reduced ability to phagocytose bacteria.

Following inhalation of DU aerosols, the deposition of particles within respiratory lymph nodes may cause the death of traversing lymphocytes due to irradiation by alpha-particles, but this is unlikely to lead to any substantial reduction in the ability of the body to combat infection (see Chapter 3 where possible radiological effects on the immune system are discussed further).

Whether there could be slight effects on immune status in soldiers with high intakes of DU is less easy to evaluate. Korényi-Both et al (1992) have described a pneumonitis (Al Eskan disease) that they associate with exposure to the very fine sand particles (0.1-0.25 µm diameter) present in the Persian Gulf. They have proposed that ultrafine sand particles can be pathogenic, not simply due to acute silicosis but to allergic hypersensitivity to the ultrafine sand associated with pathology of the immune system. The proposed immunosuppression has been suggested to be a contributory cause of Gulf War Syndrome (Korényi-Both et al 1997). Whether exposure to ultrafine sand can lead to immunosuppression is unclear but the possibility adds to the list of potentially toxic exposures, which include multiple vaccinations, squalene in vaccine components, antidotes to nerve agents, pollution from oil well fires, pesticides and rodenticides, organic solvents and perhaps DU, that together may contribute to the symptoms seen in veterans of the Persian Gulf War.

Effects on the immune system might be revealed by an increased incidence of infections, but subtle effects may not be detected. Disorders of immunity could also lead

to autoimmune disease, or an increased incidence of cancer due to reduced immune surveillance, both of which are only likely to become evident in later life, and cannot be easily predicted at an early stage.

The immune system includes a wide variety of interacting elements, which generate antibody and cellular responses. In an individual, the immune status will vary according to exogenous influences, especially infection. It is difficult, therefore, to know which measurements to apply to determine if there is an acquired defect in those heavily exposed to DU aerosols. One useful marker of immune activity is C-reactive protein (CRP) (Du Clos 2000). Serum CRP is a classical acute phase protein, which may be raised 1000-fold in response to infection, ischaemia, trauma, burns and inflammatory conditions. Production is initiated by a cytokine (IL-6) and it occurs rapidly following infection. CRP is an indicator of activation of the innate immune response, and is increased in several clinical conditions, including cardiovascular disease (Danesh et al 2000). However, in normal adults a raised level is likely to be associated with persistent bacterial infection. Failure to clear infection is an indicator of immunodeficiency.

Immunodeficiency can also be associated with a failure of cytotoxic T cells to control endogenous viruses. It is possible to monitor a decline in the ability of the immune system to regulate persistent viruses, such as Epstein-Barr virus (EBV), by measuring viral load in the blood using a quantitative polymerase chain reaction (PCR) (Ohga et al 2001).

In summary, in normal adults, measurement of CRP presents a simple and economical way of assessing a failure to control bacterial infection. Although not a specific test, normal levels would argue against damage to the immune system, and could be used as a measure of immunotoxicity. Measurement of EBV load is a more expensive test, and less widely used. A significant increase might indicate a failing T-cell response.

5.8 Reproductive and developmental effects

From the very few studies available no clear effects on reproductive health have been reported in humans. Animal studies have indicated adverse effects in rodents ingesting or being exposed via dermal contact to extremely high levels of soluble uranium compounds (WHO 2001).

Uranium has been shown to be present in the semen of veterans retaining fragments of DU shrapnel and presumably would be present in the semen of soldiers heavily exposed to DU aerosols. DU also appears in the testes of rats containing implants of DU pellets (Pellmar et al 1999a). This raises the possibility of adverse effects on the sperm from either the alpha-particles emanating from the DU or from the mutagenic activity of uranium, and

possible synergistic effects (Miller et al 1998a,b). Uranium is also known to cross the placenta (Sikov and Mahlum 1968; McClain et al 2001) and increased levels of uranium in the mother will lead to increased levels in the foetus.

Studies on the reproductive health of workers in the nuclear industry, and of survivors of the atomic bombs, show little evidence of decreased fertility, or an increased incidence of miscarriages or birth defects (Otake et al 1990; Doyle et al 2000). For example, a large study of over 20,000 pregnancies in the partners of male radiation workers at the Atomic Weapons Establishment, the Atomic Energy Authority and British Nuclear Fuels who had been exposed to radiation prior to conception showed no increase in foetal deaths or malformations. The lack of effect was seen both for workers who were only monitored for external radiation and for those monitored for both internal and external radiation. Female radiation workers exposed prior to conception had a slight increase in early miscarriages and stillbirths (Doyle et al 2000).

Effects of natural uranium on reproductive health have been observed in male mice, although at very high intakes. Daily ingestion of large amounts of soluble uranium (between 10 and 80 mg uranium per kg per day; equivalent to 700 mg - 5.6 g per day for a 70 kg man) over nine weeks had no apparent effect on testicular function or sperm development, but there were some effects on the morphology of the hormone-producing cells in the testes at the highest exposure level. A decrease in male fertility was reported but this was not related to the level of uranium exposure and its significance is unclear (Lobet et al 1991). We are not aware of any animal studies that have looked for developmental abnormalities in the progeny of uranium-exposed males.

In other studies using male mice injected with plutonium-239 and mated to untreated females, there was an increased susceptibility to leukaemia induced in the offspring by methyl-nitroso-urea (Lord et al 1998). The dose of plutonium (accumulated to three months prior to mating and averaged over the testis) which doubled the susceptibility to leukaemia in the offspring can be calculated to be around 100 mGy, ie about 2 Sv using the radiation weighting factor of 20. However, to achieve the same dose to the testes of a 70 kg man using the much less radioactive DU would require injection of about 1 kg of soluble DU.

Ingestion of 5 mg of soluble uranium per kg per day during pregnancy had no effect on sex ratios, mean litter size, body weight or body length of the newborn mice at birth or during the subsequent three weeks (Domingo et al 1989a). When treated males (ingestion of 25 mg uranium per kg per day for 60 days) were mated with treated females (25 mg uranium per kg per day for ten days prior to mating and subsequently), there were

significant numbers of dead offspring per litter at birth and at day four of lactation. Also, the growth of the offspring was always significantly less for those derived from the uranium-treated animals (Paternain et al 1989).

Doses of 5-50 mg of soluble uranium per kg per day in food during pregnancy have been shown to reduce foetal body weight and body length, and to produce developmental defects including cleft palate and skeletal abnormalities (Domingo et al 1989b). These effects were particularly apparent at the 25 and 50 mg per kg dosages but some effects were apparent at 5 mg per kg. Developmental effects and malformations were also observed in mice born to mothers given daily subcutaneous injections that resulted in severe maternal toxic effects including death (Bosque et al 1993). The significance of these effects in mice are unclear as they occur at high intakes of soluble uranium that are the equivalent of between 250 mg and 2.5 g per day for a 50 kg (eight stone) woman.

There are uncertainties in extrapolating from animal studies to humans and there is a possibility of effects on reproductive health for soldiers who have high levels of exposure to radiation; careful epidemiological studies are required. Dr Pat Doyle and colleagues are investigating the reproductive health of male and female UK Gulf War veterans and the health of their children, although the results of the study are not yet available. The study compares those that served in the Gulf with a similar group of military personnel who were not deployed in the Gulf. The endpoints being examined include infertility, foetal loss, low birth weight, congenital malformation and childhood illness. If there is an effect on reproductive health, it will not be possible to establish whether this is due to DU or to any of the other potentially toxic exposures in the Gulf War.

6.0 Kidney uranium levels and kidney effects from DU intakes on the battlefield

All of the available information indicates that the most serious adverse effects from the chemical toxicity of uranium will be on the kidney. In Part I of this report, biokinetic models were used to estimate the amounts of uranium reaching the kidney for the intakes of DU that might occur on the battlefield. Two estimates were obtained for each battlefield scenario. The 'central estimate' used the most likely values of the amounts of DU that could be inhaled (or ingested), and the most likely of the rates of dissolution of the inhaled or ingested DU. The 'worst-case estimate' used values of intakes of DU that are unlikely to be exceeded, and values of the dissolution rates of inhaled or ingested DU that maximise the amount that reaches the kidneys. The estimated maximum concentrations of uranium in the kidneys for different battlefield scenarios are given in table 7.

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Table 4. Average annual effective dose from natural sources

Cosmic rays	0.32	mSv/year
Terrestrial gamma rays	0.35	mSv/year
Internal long-lived radionuclides	0.27	mSv/year
Internal radon and short-lived progeny	1.20	mSv/year
Internal thoron and short-lived progeny	0.10	mSv/year
Total	2.24	mSv/year

Table 5. Estimated effective doses from DU exposure scenarios

	Central estimate	Worst-case
Level I exposure	22 mSv	1,100 mSv
Level II exposure	0.52 mSv	440 mSv
Level III exposure to smoke plumes	0.007 mSv	4.0 mSv
(Level III exposure to all pathways)	(0.09 mSv)	(66 mSv)

received within the first year, corresponds to about ten times the average received in one year from natural sources of radiation. The Level II and III scenarios give central estimate doses that are lower than the annual natural dose. The exposure from the Level I worst-case exposure is about five hundred times the annual natural dose, whereas the worst-case Level II and Level III exposures give, respectively, doses that are two hundred times, and twice, the normal annual levels of radiation.

3.8 Chemical versus radiological action of depleted uranium

Our analysis above assesses only the radiological risk from DU, following standard internationally accepted methods. We have not included chemical effects from DU, either in isolation, or in combination with the radiation. Toxic chemical effects of uranium on the kidney and other organs will be included in our second report. However, the potential for effects (including cancer) resulting from the chemical action of uranium at the DNA and cellular levels is considered here.

Experiments with a human osteoblast-like cell line *in vitro* have shown that soluble or insoluble DU can induce malignant transformation of the cells (Miller et al 1998a, 2001). DU has been reported also to damage the genetic material of cells, inducing DNA strand breaks and chromosome rearrangements (Miller et al 1998a, 2000). Studies of rats with embedded DU pellets have shown changes that are associated with carcinogenesis, and the uranium-containing urine was able to produce mutations in bacterial systems designed to identify chemicals that can damage the genetic material (the Ames bacterial

reversion assay; Miller et al 1998b, 2000). Although many, or all, of the above effects may be expected from the radiation exposure from DU, there are reasons to suggest that they may be chemical effects as they were very much more frequent than might be expected from the very small proportion of cells that were hit by an alpha-particle. Similar frequencies of malignant transformations are observed with the non-radioactive heavy-metal carcinogens nickel and lead (Miller et al 1998a). The other indicators of damage to the genetic material are also observed with nickel and its alloys (with tungsten and cobalt), although none is detected with the inert metal tantalum (Miller et al 2000). In the vicinity of particles or fragments of DU, cells will be subject to these putative chemical effects of DU which might increase their sensitivity to the occasional passage of alpha-particles, or the more frequent but less damaging beta-particles or gamma-rays. Further studies would be required to examine the possibility of synergy between the chemical effects and radiation effects of DU.

3.9 Embedded shrapnel

The dose and dose-rate to tissue in immediate contact with an embedded fragment of DU are extremely high. As evaluated in annexe B, tissue in contact with a piece of DU shrapnel is irradiated with alpha-particles at a dose-rate of about 1300 Gy per year (ie 3.6 Gy per day)³. The alpha-particle dose-rate decreases gradually away from the surface, until at about 30 micrometres distance it drops to zero because of the small ranges of the alpha-particles. In this very thin irradiated shell of tissue most of the cells would be sterilised on a daily basis. For example, this dose would correspond to about

³ At these very large doses, to only a small volume of tissue, we have directly used the absorbed dose to the irradiated tissue (in gray; Gy), as the averaging procedure and the assumptions underlying the concept of equivalent dose (in Sv) may be less appropriate in this case.