ECRR

Uranium and Health

The Health Effects of Exposure to Uranium and Uranium Weapons Fallout

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Explosion plume, Khiam, Lebanon, 25 July 2006
Photo: Lotfallah Daher,

Uranium, and Uranium Weapons

For there is nothing hid that shall not be manifested;
neither was anything kept secret, but that it should come abroad
Mark 4,22

1 Introduction

The element Uranium is the basis of and parent of almost all releases of radioactivity to the environment, yet curiously, until it began to be employed as a weapon, it had been quite neglected as a hazardous component. It is not measured routinely near nuclear power stations or reprocessing sites. It is treated as if it were natural which of course it is, but its concentration in these places, and the form it is released in is not.

The intense and increasing interest in the health of the troops who participated in the first Persian Gulf War in Iraq, and later those who served in the Balkans, where Uranium weapons were also used, and of course the civilian populations of those areas have resulted in evidence that the genotoxicity of Uranium is far greater than the military who used it, and the states which sanctioned this, believed. Despite the increasing evidence of its anomalous propensity for harm, from epidemiology and from laboratory and theory, the ICRP risk model, here as in everywhere else in radiation protection, is used to deny the evidence and to sanction its continued use as a weapon of war. As with the fallout from bomb tests, Chernobyl and the child leukemias near power stations, clear evidence of harm from exposure to Uranium is denied on the basis of deductive logic, that the absorbed doses are too low to cause any measurable effect. By 2006, when massive population-based evidence that the exposures to so-called Depleted Uranium, DU were causing harm, and evidence from laboratory studies and theoretical research had also emerged, UNSCEAR, in their 2006 report allowed 11 lines on one page in their 400 page report to the consideration of DU effects. UNSCEAR based its dismissal of any problem with Uranium exposures on three citations, desktop reviews, the RAND corporation 1999 report (Harley *et al* 1999), the US Institute of Medicine 2001 report and that of the Royal Society in 2001. None of these reports were peer-reviewed, and the RAND corporation is believed to be closely associated with the US Pentagon. All were selective in their references. And all were out of date. None of these could deal with the particulate nanoparticle inhaled Uranium from weapons fallout, since no-one had studied it. Y*et al*l three (and also countless reports from agencies like WHO) employed the ICRP model to show that the doses were too low.

Despite the many studies which will be reviewed below and which were accessible to UNSCEAR, its 2006 report (which appeared in 2008) states (p53):
There appear to be several possible reasons why Uranium is not. . . considered a human carcinogen (by the Institute of Health): Uranium is not very radioactive (having such a long half life of billions of years, 238U

decays very slowly) and its chemical properties are often such that any inhaled or ingested Uranium is excreted rather quickly from the body.

By 2004, the way that official agency reports ignored the increasing peer reviewed evidence that Uranium was much more genotoxic than its radioactivity suggested became so embarrassing that the senior radiation health advisor to the WHO, Keith Baverstock wrote a paper with Carmel Mothershill on the issue to the Director General. He was sacked but the paper was later published (Baverstock 2005).

The scientific investigation of DU gives a curious condensed echo of the earlier investigations into the nuclear site child leukemias. This is not surprising given the political consequences of having to concede that the low doses of DU, conventionally assessed, were capable of causing such graphic and appalling genetic effects on populations exposed to the dust. For if this could happen with Uranium, it means that all of the basic equations and assumptions of the risk model are wrong. The matter has been painstakingly researched and reviewed recently by an American academic, Paul Zimmerman whose conclusions, independently gained by an academic, closely agree with the ECRR thesis developed in 2003 and in the present 2010 report (Zimmerman 2008).

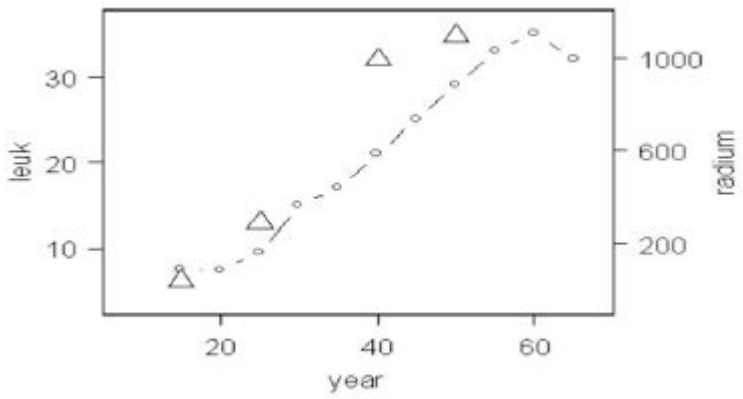
It is an interesting fact that the military and the nuclear industry internally take Uranium exposure very seriously as far as handling the material is concerned. Spills, even small ones have to be dealt with, with all the rigours associated with contamination by radioactive material. The same is true for the military, who publish internal documents warning of the health effects. However, as soon as the Uranium is shot from the gun and has contaminated the theatre of war, it suddenly becomes benign, in all the reports of the issue, and in the denials of the military and its risk agencies and those of the governments involved.

The effects of exposure to Uranium are not, of course, restricted to DU and passive weapons fallout. Uranium is increasingly contaminating the environment, near nuclear sites, near isotope separation plants, near fuel manufactories, near Uranium mines and in atomic and thermonuclear weapons fission fallout, near and remote from the test sites. Uranium is increasingly found in food and drinking water as it is a significant component of agricultural fertilizer. It is therefore also found near fertilizer factories and phosphate mines and in the transportation of phosphate ore and its agricultural products (Eisenbud and Gesell 2000, Busby and Schnug 2008). The mining of Uranium began at the beginning of the last century. Also beginning at the same time was a new disease: childhood leukemia, which is believed to result from a mutation *in utero*. The temporal correlation between the incidence of this disease and the production of Uranium (modeled as Radium) is startling, and is shown in Fig 1 below. Despite this, Uranium seems to have been forgotten in investigations into contamination near nuclear sites, diseases associated with weapons fallout, Chernobyl effects. It is the invisible substance. Measurements made new nuclear sites will show concentrations of exotic isotopes, vanishing concentrations of Plutonium in fish, but few

measurements are made of the Uranium emerging from the nuclear sites. In the COMARE analysis into the Sellafield child leukemias, it was concluded that although the doses from Plutonium to the tracheobronchial lymph nodes of the children were high, the doses from natural radionuclides were higher, and so the nuclear site could not be responsible, even if these were the source of the disease. After Chernobyl, large amounts of Uranium were released as fuel particles, but no measurement of Uranium is to be found in any of the reports on Chernobyl fallout.

ECRR set up a sub-Committee to examine the issue of Uranium weapons. This report presents a brief account of the findings, reviews the evidence for DU and Uranium effects and makes recommendations.

Fig 1 Trend in child leukemia mortality (line) and world Radium production (g) (*Source: Busby 2002 acknowledging Bramhall R)*



2 *Depleted Uranium: Uranium weapons.*

Depleted Uranium is a by-product of the nuclear industry where the fissile isotope U-235 in natural Uranium ore is concentrated to produce reactor fuel consisting of 'enriched Uranium'. The isotope discarded by this process is Uranium 238 which is generally classed by the risk agencies as a low radiation hazard material owing to its long half life (4.5×10^9 y) and its weak gamma emission of 48keV. However, it is an alpha emitter and thus poses an ingestion risk owing to the high ionization density of alpha tracks and their high biological effectiveness in inducing mutation. In addition, there is a risk from the beta-emitting daughter isotopes Thorium 234 (β 0.26MeV, half life 24 days) and Protoactinium-234m (β; 0.23MeV, half life 6.75 hours) which decay through one another to Uranium-234, also an alpha emitter with a half life of 2.47×10^5 years. The overall activity of Uranium 238 therefore increases as soon as it is produced due to ingrowth of the beta daughters and by 30 weeks these are in total secular equilibrium. The activities per kilogram are given in Table 1 below. Uranium-238 has a low specific activity, $12MBqkg^{-1}$ which means that, unlike most radionuclides which are considered

in risk analyses, at environmental concentrations which represent a radiological exposure, the chemical concentration is significant. 1Bq is 83μg and $1Bqg^{-1}$ in tissue represents a concentration of 3.5×10^{-4} M which is a significant physiological concentration.

Over centuries, the specific activity of U-234 should be the same as the parent U-238, and thus the environmental concentrations of these isotopes are generally the same if the source is natural. The specific total activity is thus about 37MBq/Kg. It should be pointed out that DU material recently found in battlefields in Europe contains small quantities of isotopes of Plutonium, Neptunium and other fission products: thus the source of this DU is refinement of nuclear reactor waste. However, the quantities are very small and are not considered by the Committee to be of serious radiological significance. More curious are reports of weapons which have isotopic signatures showing enriched Uranium, first reported in Lebanon, then Gaza, and most recently in analysis of biological materials from a veteran of the Bosnia theatre in 1996 (Busby and Williams 2006, 2008, Ballardie *et al* 2008). Indeed, tables of isotope ratios in environmental post conflict samples published by the United Nations Environment program UNEP show clear evidence of enriched Uranium usage in Bosnia (UNEP Bosnia report 2002). (UNEP have consistently denied finding enriched Uranium, and this mistake was quickly covered up when pointed out: the table has been taken off the UNEP website). For this reason, the ECRR prefers the term Weapons Derived Uranium (WDU) to describe the issue.

Table 1 Specific Activity (MBq/kg) in decay of U-238 in Depleted Uranium to U-234 and ingrowth of daughters

Weeks	**U-238 (α,γ)**	**Th-234 (β)**	**Pa-234 (β)**	**U-234 (α,γ)**
0	12.43	0	0	0
5	12.43	7.89	7.84	0.001
10	12.43	10.77	10.75	0.004
20	12.43	12.21	12.21	0.01
30	12.43	12.4	12.4	0.017

Owing to the high density of Uranium, (19 $g.cm^{-3}$ metal and 10.96 g. cm^{-3} for the dioxide) and the fact that the metal is pyrophoric (burns in air) the substance is used in the manufacture of armour piercing shells, missile nose cones and penetrators. It is also employed in certain ballast materials in some aircraft (e.g. helicopter rotors, commercial aircraft counterweights). As a weapon, on impact, the DU burns to a fine aerosol of ceramic Uranium oxide particles of mean diameters from about 1000nm (1μ) down to below 100nm depending on different study results and distances from targets. These particles are long lived in the environment (and in tissue), and can travel significant distances from the point of impact up to thousands of miles (Busby and Morgan 2005). They become resuspended in air, are found in air filters in

cars at some distance from the attacks, and are respirable. Because their diameters are so small, below 1000nm, they are able to pass through the lung into the lymphatic system and in principle can lodge anywhere in the body. Here they may remain for several years in the same place. The biological half life of such particulate Uranium is unknown but is very long. According to research with animals it can be greater than 13 years (Royal Society 2001).

A single Abrams 120mm tank shell contains about 3kg of DU (111MBq of radioactivity) and there is 275g in a 30mm GAU3A A-10 Thunderbolt Gatling Gun round. These munitions were used in Gulf War 1. More recently evidence has emerged that hard target warheads have been deployed on cruise missiles and bunker busting bombs, each containing up to one tonne of Uranium. Estimates of the quantity of Uranium used in Gulf War 2 in 2003 are as high as 1700 tonnes (Al Ani and Baker 2009).

Military penetrators explode on impact with hard targets with about 80% conversion to micron diameter Uranium Oxide particles of a 'ceramic' nature. These particles are highly mobile and extremely long lived in the environment, owing to the very high degree of insolubility of Uranium Oxides UO_2 and U_3O_8. They can be inhaled and the sub-micron diameter particles are translocated from the lung to the lymphatic system, building up in the tracheobronchial lymph nodes and potentially able to circulate everywhere in the body since they incapacitate macrophages (Kalinich *et al*. 2002). They can pass through the skin and through most gas-mask filters. Alpha and beta disintegrations from these particles cause very high and repetitive doses to cells local to the range of the disintegration i.e. about 30 microns for the alpha and 450 microns for the beta tracks. The instantaneous (t = 0) dispersion (spectrum) of particle size from DU impacts was obtained using special cascade impactor collectors at the US Aberdeen proving grounds by Glissmeyer *et al.* (1979). The mean geometric diameter for particles collected behind the target was found to be 0.8μ. More recently, the EU SHER (2010) report states that 31% of the particles have mean diameters below 0.18μ. Particles of this size are effectively gaseous and can pass through the skin and penetrate to any part of the body. They are therefore not comparable to historic studies of Uranium exposures since such concentrated forms have never existed and have never been studied: they are completely new exposures that have to be assessed *de novo*.

The reason that DU is employed is that the weapons are astoundingly successful and have revolutionised warfare, rendering the tank and its armour useless. In addition, its use represents a route for the nuclear industry to rid itself of a waste product which would otherwise be expensive to dispose of. But the downside is that the material clearly represents a radiation hazard which is indiscriminate: battlefields are going to be contaminated and civilian populations are going to be exposed.

Apart from the evidence that Uranium is far more genotoxic than is modeled, which will be reviewed below, there is an immediate argument from quantity of radioactivity. The average Natural Uranium content of soil is about 10-20 Becquerels per kilogram, including all the Uranium isotopes. The average excretion of Uranium in urine is less than 10nBq l^{-1} (in the UK) as a

result of absorption of natural Uranium in food and water. Pure Depleted Uranium contains about 12.4MBq of U-238 per kilogram and in Kosovo, some soil samples analysed by the United Nations Environment Program (UNEP) contained 250,000Bq/kg (UNEP 2001, Annex). The 350 tonnes of DU used in the first Gulf War represent 4.3 TBq (4.3×10^{12} Bq) of Uranium alpha activity (13.0×10^{12} if the radioactive beta emitting daughter isotopes are included). The 1700 tonnes that were used in the 2003 war, represents 63 TBq of activity dispersed mainly into a populated area of perhaps 100km^2. This gives a mean density of deposition of radioactivity of 630,000Bq/m^2. These sums are instructive and are collected together in Table 2.

It is possible to find a comparison to illustrate the overall radiological situation. As an alpha emitter and long-lived environmental particle Uranium can be compared with Plutonium-239 a radionuclide released by Sellafield and a major contaminant of the Irish Sea. Plutonium in the environment is also in the form of sub-micron sized oxide particles. The comparison is made in Table 3. Like DU, these Plutonium Oxide particles are long lived and mobile. Plutonium from Sellafield has been measured in autopsy specimens across the UK, in sheep droppings on the east coast of England 100 km from Sellafield at the same latitude and even in the teeth of children up to 200 km from the site in south east England. U-238 has a very long half life, 4500 million years, so owing to its much shorter half life of 24,100 years, the specific activity of Pu-239 is far greater. It is 2.3TBq/kg. But this means that 350 tons of DU (or 4.30TBq of U-238) is equivalent in activity (quantity of radiation) to about 2 kg of Plutonium-239. The ethical dimensions of the intentional scattering of 2kg of Plutonium-239 over a populated area are easy to imagine.

Table 2 Mean density of deposition of radioactivity from DU in the two Gulf Wars and Kosovo including decays from U-238 and beta daughters Pa-234m and Th-234 compared with other radioactive contamination.

Event	**Activity released or estimated deposited**	**Mean activity density Bq per square metre (area)**
10 tons of DU in Kosovo	0.37TBq	3700
350 tons of DU in Iraq 1	13 TBq	130,000 (into 100 km^2)
1700 tons of DU in Iraq 2	63TBq	630,000 (into 100 km^2)
Global weapons fallout Strontium-90 (Sr-90) Northern Hemisphere lat. 50-60deg (UNSCEAR, 2000)	73.9PBq	460
Chernobyl 30km Exclusion Zone *measured* Sr-90 (IAEA)		37,000 to more than 111,000
UK North Wales Radioactive Sheep restrictions *measured* Caesium-137 (Cs-137)		15,000 to 30,000
UNSCEAR definition of contaminated area. (Cs-137)		> 37,000
Irish Sea cumulative Plutonium from Sellafield 1952-1996 [Busby, 1995]	1350TBq	20,000

Table 3 Comparing Plutonium-239 and Uranium-238 in the environment

	Uranium-238	**Plutonium-239**
Environmental form	0.2-2μ oxide particles	0.2-2μ oxide particles
Density of material $g.cm^{-3}$	(UO_2) 10.9;(U_3O_8) 8.3	(PuO_2) 11.46
Solubility	Insoluble	Insoluble
Environmental Longevity	Long lived	Long lived
Main radioactive emissions	Alpha + beta + beta	Alpha
Alpha particle energy	4.19MeV	5.15MeV
Half life	4.51 billion y	24400y
Specific activity	37.2MBq/kg ($\alpha + \beta$)	2.3TBq/kg (α)
Main present contamination source	DU	Fuel reprocessing e.g. Sellafield
Mass for equal activity	175 tons	1kg

3 The evidence of harm from Uranium exposures

Uranium oxide nanoparticle exposure from weapons does not represent the same kind of hazard as Uranium exposures in people living in high background Uranium areas, nor those who work as Uranium miners and machinists. The exposures are quite different in quality and type. Comparisons of miners exposed to Uranium ore dusts will compare those who inhale particles which have very low concentrations of Uranium and which are fairly large. In Gulf war veterans and civilian populations the Uranium is almost pure. The local doses to and concentrations in tissue will be thousands of times greater in the case of the weapons exposures and the much smaller particle sizes will ensure the rapid internalisation of the uranium, through completely evolutionarily novel routes, though the lungs or directly through the nose to the mid brain or even through the skin. The nanoparticles will penetrate individual cells. Thus the highest concentrations will begin in the cells, where the DNA is, and concentration will fall towards the blood supply reservoir, the opposite of what happens with those who ingest uranium contaminated solutions of food. Comparing Uranium urine excretions or blood concentrations to get an idea of similar levels of exposure and making calculation on the basis of average dose conversion coefficients will also be invalid for this reason. It is an averaging problem, like all the others associated with comparing external and internal irradiation. Nevertheless, because there are overlaps, the effects of exposure to Weapons Derived Uranium will be discussed in parallel with other Uranium exposures. We should expect many of the effects found but at much lower apparent doses in the case of WDU. The above *caveat* should be borne in mind.

3.1 Health effects: epidemiology

Uranium is primarily genotoxic. Exposure to Uranium causes genetic and genomic changes and therefore impacts most organs in mammals. Particularly targeted are the kidney, the brain and the reproductive system. A list of reported conditions associated with Uranium exposure is given in Abu Quare and Abou-Donia 2002 and Craft *et al* 2004. Bertell 2005 has reviewed the area and drawn attention to significant gaps in knowledge and recently a number of authors have discussed the problem in a UN report (UNIDIR 2008).

The teratogenicity of exposure to Uranium weapons aerosols is reviewed by Hindin *et al* (2005). Many reports of congenital defects in children born in Iraq following the first and 2nd Gulf wars (e.g. Hamburg 2003) have not been followed up by any studies by WHO or any responsible authorities. The main reported illnesses and conditions associated with exposure to Uranium are listed in Table 4

It will be apparent that Uranium exposure will have a profound effect on the health of any population, and that the range of effects covers the entire spectrum of disease.

Table 4 Illnesses and conditions reported in the literature to be associated with exposure to Uranium.

Mutagen: Reproduction: teratogenic and genotoxic; causes lower fertility, miscarriages, heritable defects in children, stillbirths, childhood cancer and leukemia. Oestrogenic mimic with responses in humans and animals.
Mutagen: Cancer and leukemia increases in those exposed and their offspring in humans and animals.
Kidney disease generally, problems below 100ng/g contamination, glomerular and tubular lesions, tumorigenic changes, creatinine levels alter with dose, glomerular structures altered, IgE and IgG nephropathy, persistent structural and functional and functional damage.
Blood; cytotoxic and leukemogenic; reduction in red blood cells.
Brain; targets the brain and causes wide range of effects associated with damage to deep brain and brainstem fuction, effects shown by objective tests. Basis of the Gulf War syndrome. Weapons Uranium particles enter the mid brain directly from the nose.
Concentration: circulates as uranyl ion which has the same affinity as Calcium, therefore binds to and targets DNA, nervous tissue, bone, sperm. For this reason most organs will be affected (mitochondrial DNA affecting energy conversions in cells).
Chromosome aberrations found in those exposed to Uranium; the effect is out of proportion to the ICRP calculated dose for external radiation.
Mutagen: retinoblastoma rates highest in Navajo tribes living on Uranium tailings; rates also high in offspring of Sellafield workers and near Rocketdyne site near Los Angeles contaminated with Uranium.
Mutagen: Sex ratio effects in offspring of male Uranium miners Inflammation: associated with oxidative stress at site of Uranium
Carcinogen: cancer increases in BNFL Uranium fuel-element workers

Despite this, there have been virtually no epidemiological studies carried out of populations exposed to weapons Uranium. The one exception is a study carried out at the request of the Italian military into cancer in the Balkans peacekeepers. The first report showed a significant excess of lymphoma (equivalent to 8-fold) in peacekeepers stationed in Bosnia and Kosovo (Italian report 2001). More recent investigation of the data shows that the cancers were mainly from those who served in Bosnia, making the relative risk more like 14-fold. A recent update on the situation seems to have been kept confidential; reports are that levels of cancer in this cohort are startlingly high and checks are being carried out. No credible study of cancer or birth defects in UK or US veterans has been published although parliamentary questions have elicited data which show an increase in lymphoma in UK veterans of the 1st Gulf War. Recently, a coroner's jury in the UK found that a British Gulf war veteran, Stuart Dyson, died of colon cancer because of exposure to Depleted Uranium in Iraq (Dyson 2009) and the Minister was informed under Section 43 of the UK Coroners Act. Evidence was taken from ECRR and from scientists from the UK Ministry of Defence but clearly the jury believed that the cancer was caused by the exposure.

Cancer data from Sarajevo in Bosnia has been reported, and show remarkable increases (up to 20-fold) in the incidence at many sites (Hamburg 2003). A cohort study of cervical cancer in Greece concluded that exposure to Uranium aerosols was the cause of a statistically significant increase in the disease those exposed as shown by cervical smear screening results (Papathanasiuo *et al* 2005). There have also been many reports of high levels of cancer in Iraq following the bombing both in 1991 and later in 2003, but no systematic study has been published. An early study by McDiarmid *et al* (2002) found no evidence of increased risk of cancer in US veterans of the first Gulf war, though ill health from many conditions (generally, Gulf War syndrome) was reported.

Gulf war syndrome itself was examined in a sophisticated Factor Analysis by Haley *et al* (2000) in the USA, funded by Ross Perot. The syndrome encompasses many conditions, problems which the military and their advisors in the UK blamed on stress, but which Haley identified as having in common that they resulted from damage to the brainstem and lower brain housekeeping functions. Haley went on to show that this was the case by carrying out a magnetic resonance imaging case control study of US veterans. The P32 and H1 studies identified significant loss of viability in cells in the brain associated with the housekeeping functions of the brain which were manifesting themselves as Gulf War syndrome. Haley was not aware of the targeting of the brain and lower brain by Uranium and blamed the effects he found on exposures to organophosphates. However, research which was carried out some years after Haley's work showed the profound targeting of this area of the brain by Uranium, and the fact that inhaled Uranium has a direct access to these parts of the brain through the olfactory lobe (see below).

The situation in Iraq has become serious: genotoxicity of Uranium exposures has resulted in a catastrophic increase in cancer and congenital disease. This was reported at the September 1998 General Conference of the IAEA and has been comprehensively reviewed by Al Ani and Baker (2009). In the same volume, these authors review other evidence of increases in genetic and genomic based disease in those parts of Iraq contaminated with Uranium and cite the many studies that report the levels of contamination and also the health indicators. However, none of these reports has been considered by the risk agencies and in addition no western based study has been carried out on the populations of Iraq in order to investigate the concerns. The Committee is currently engaged in a study of cancer and congenital birth defects in Iraq.

Statistically significant Uranium effects have been reported at the Springfields fuel fabrication plant in the UK (McGeoghegan and Binks 2000). A strong association, related to Uranium exposure, was reported for Hodgkin's lymphoma and Non Hodgkin lymphoma, though the authors did not believe the relation was a causal one since the absorbed doses were too low.

3.2 Genetic damage: chromosome aberrations

Chromosome aberration analysis can be used as a flag for earlier exposure to ionizing radiation. Indeed, it is possible to reconstruct the doses and make some assumptions (on the basis of the types of chromosome damage, dicentrics and centric rings) on the type of exposure, whether low or high LET (Hoffman and Schmitz Feuerhake 1999).

Unexpectedly high levels of chromosome aberrations in Uranium miners in Namibia were reported by Zaire *et al* 1997. Studies of chromosome aberrations in a set of Gulf War veterans suffering from Gulf War syndrome were also examined by Schroeder *et al*, 1999. Results showed levels of damage consistent with earlier exposures of about 150mSv although clearly these veterans could not have been exposed to more depleted Uranium than would account for a committed dose of 100μSv. Both these studies identify an error in the calculation of dose from the Uranium exposures of approximately 1000-fold. It should be noted that chromosome damage leaves the body with a half life of about 2 years, yet these Gulf veterans were showing this damage some ten years after the exposures, suggesting some depot of Uranium which was long lived. The Royal Society (2001) cite references to support the view that the half life of some types of Uranium in the body is longer than 10 years and may be considered to be perhaps indefinite. Chromosome aberrations have been found in a case control study of New Zealand Atomic test veterans (also exposed to Uranium at the test sites) some 40 years after the exposures.

Chromosome aberration analysis in Bosnia has shown significant Uranium exposure effects in an ecological study by Ibrulj *et al* (2007). The study evaluated peripheral lymphocytes from 84 individuals split between inhabitants of Hadzici where NATO strikes involved Uranium (and UNEP measurements showed presence of Uranium in 2002) and a control area where there was little exposure. Results showed a statistically significant increase in chromosome aberration frequencies in the exposed group in 2007, some ten years after the attacks. Micronuclei were also increased in peripheral lymphocytes in the same populations exposed to Uranium (Ibrulj *et al* 2004).

Hadzici in Bosnia was also studied by Krunic *et al* (2005) to evaluate the genetic damage to those who were exposed to Uranium weapons. The authors were able to show excess micronuclei in peripheral lymphocytes compared with controls from west Herzegovina.

In cell culture experiments, Miller *et al* 2002 were able to induce dicentric chromosome changes and neoplastic transformation in human cells exposed to depleted Uranium at 50μM (i.e.200ng/l) for 24hrs. This is a very low concentration and the presence of alpha emissions per cell is stochastically absent. Using different Uranium isotopes the study showed that there was a specific activity related effect and the conclusion was that radioactivity can play a role in the neoplastic transformation frequency. Nevertheless, the exposure was so low that this result supports the argument for secondary photoelectron enhancement outlined in Chapter 6 and reviewed below.

From these studies it can be concluded that Uranium exposure causes chromosome damage and micronuclei formation in human populations at

levels of radiation exposure (conventionally assessed) which are more than 1000 times too low to explain these effects. The recent report by Darolles *et al* (2010) is of interest. The authors report differences between enriched and depleted Uranium in cell culture studies at quite low concentration levels. Reduced to basics, depleted Uranium causes aneuploidy and micronuclei formation whereas the enriched Uranium causes chromosome aberrations. This would, of course, be an expectation of the two types of action implicit in the discussions of mechanism above. Owing to the higher activity of U-235 the main chemical species in solution is uranyl U-238 in both the enriched and the depleted Uranium experiments. Therefore there will be significant binding of the U-238 uranyl to the chromosomes resulting in destruction of whole chromosomes through the photoelectrons emitted throughout their length at the binding sites of the U-238 atoms along the phosphate backbone. The U-235 effects are then the normal alpha track high ionisation effect where a chromosome is cut (double strand break) and recombines anomalously to give the aberrations which are found. The authors (who are associated with the French IRSN) point out that the aneuploidy produced by U-238 is associated in other reports with cancer induction and they call for a reassessment of the carcinogenicity of Uranium.

3.3. Reproductive and transgenerational genetic effects

The teratogenic effects of Uranium exposures have been reviewed by Hindin *et al* (2005) who concluded from the evidence that Uranium represented a teratogenic hazard. Certainly many reports have emerged from areas where Uranium weapons have been employed showing that there follow major increases in stillbirth, and congenital malformations of a particularly alarming and unusual kind. Despite these, no credible western studies have been commissioned or carried out. A case control study of UK Atomic Test Veterans children and grandchildren identified a 9-fold excess of congenital conditions in the children and an 8-fold excess in the grandchildren relative to national controls (Busby and de Messieres 2007). These veterans were exposed mainly to Uranium since their gamma film badge doses were in general known and analysis showed the existence of significant quantities of Uranium on the test sites.

A review of the reproductive toxicity of natural and depleted Uranium by Domingo (2001) concluded that Uranium was a development toxicant when given orally or subcutaneously to mice. Decreased fertility, embryo toxicity, teratogenicity and reduced growth were shown to occur. Paternain *et al* (1989) had already showed developmental and birth outcome effects in mice at doses as low as 5mg/kg with no zero effect dose. A study of the effects of Uranium on the hatching success, development and survival in early stages of zebrafish (*danio rerio)* was reported by Bourrachot *et al* (2008). The authors used levels of depleted Uranium in the water of 200-500μg/l (about $3Bql^{-1}$) but also employed a higher specific activity Uranium isotope U-233 to examine the effects of what they believed to be chemical rather than radiological stress. Both regimes showed significant developmental effects at the lowest

exposures. 250μgl^{-1} showed a 43% reduction in median hatching times relative to a control. A 15 day exposure to this concentration of depleted Uranium gave a 100% mortality at the pro-larval stage. The more radioactive U-233 was more effective, but both isotopes showed the effects at this very low concentration. The radiation doses at which this was occurring are vanishingly small and would not be considered harmful on the basis of current risk models.

Raymond-Whish *et al* (2007) found that drinking water below the US EPA standard caused estrogen receptor dependent responses in female mice. The authors exposed pregnant female mice to drinking water containing from 0.5 μgl^{-1} to 28mgl^{-1} and found estrogen receptor effects including selective reduction of primary follicles, increased uterine weight, greater uterine luminal epithelial cell height and other conditions. Mouse dams that drank the Uranium containing water had morphologically normal pups but these had fewer primary follicles than pups from dams that drank normal water.

3.4 Kidney

The kidney has been identified as a target for Uranium toxicity by many studies; the early research is reviewed in the Royal Society reports (RS2001, 2002). More recently interest has followed concerns relating to weapons exposures and research has focused on the levels needed to produce nephrotoxic effects. A number of relevant studies are listed in Table 5.

A most relevant and interesting report by Ballardie *et al* 2008 presents the results of a comprehensive medical and physical analysis of a veteran of the Balkans who presented with a range of kidney conditions and many Gulf war syndrome conditions. Rather than assuming that this man's spectrum of conditions was a result of stress, a team of doctors and scientists at the Manchester Royal Infirmary and the University of Sheffield set about analyzing everything they could in order to try and discover the cause. By biopsy analysis they discovered that his kidney was contaminated with enriched Uranium, which was uniformly disseminated throughout the mitochondrial tissue. Treatment with heavy metal chelating agents effected a cure. This is a major piece of evidence in the arguments which the Gulf War and Balkans veterans have regarding the origin of their ill health and was significant in persuading the jury about causality in the above-mentioned coroner's inquest on Stuart Dyson who also suffered from Gulf War syndrome before dying prematurely from colon cancer.

Table 5 Recent studies of relevance to the effects of Uranium on kidney structure and function

Study	Results
Prat *et al* 2005	Identified a set of 18 genes which were deregulated following exposure to Uranium; the Calcium pathway is heavily implicated; nephroblastoma genes implicated
Berradi *et al* 2008	Rats exposed to 40mg/l DU in water for 9 months. Kidney deterioration and lower red blood cell counts (renal anemia).
Goldman *et al* 2006	Investigated effects of DU on rat kidney brush border vesicles. Uranyl at 140μg /mg protein reduced ability to transport glucose.
McClain *et al* 2002	Effects of embedded fragments of DU (shrapnel) in rodents. Uranium from implanted fragments found in bone, kidney, muscle and liver distant from the site of implant. Alters neurophysiological parameters in rat hippocampus, crosses the placental barrier, enters foetal tissue. Decreased rodent litter size when animals bred 6 months after implantation. No kidney effects found suggesting adaptation.
Fukuda *et al* 2006	Toxicity and biochemical markers in rats exposed to Uranium at 0.2, 1 or 2μg/g animal. Measurable changes in many markers in bone and kidney at the lowest doses.
Zhu *et al* 2008	Renal dysfunction after long term chronic exposure to Uranium pieces surgically implanted in rats.
Zimmerman *et al* 2007	Clinical chemistry and microscopic renal effects in rats exposed to single injection IM of 0.1, 0.3 and 1.0 2μg/g animal. Nephrotoxocity seen at all doses.

3.5 Brain

The effects of Uranium on the brain have only recently emerged. As already outlined above, the studies by Haley demonstrated a link between lower brain function and the spectrum of conditions which make up Gulf War syndrome. Inhalation of Uranium nanoparticles from the weaponised aerosols provides a direct route to the lower brain through the physiological connections with the nasal passages and olfactory bulb. The French (IRSN and other) studies were perhaps the first to show the accumulation of Uranium in nervous tissue, to which it seems to have an affinity, probably because of the similarity of the uranyl ion to Ca^{++}. Monleau *et al* (2005) of the IRSN laboratory in France showed that Uranium concentrations in the brains of rats exposed by inhalation were as follows: olfactory bulb> hippocampus> frontal cortex> cerebellum. Uranium is normally excluded from the overall system by a low gut transfer factor. Evolutionarily there will never have been a period when aerosols of pure Uranium existed in the environment and even Uranium miners will not be exposed to the same extent since the dusts in the mines have very low Uranium content. A list of recent studies is given in Table 6.

It is clear from the results of Lestaeval *et al* 2005 that at levels where there is no nephrotoxicity, there are measurable changes in behaviour in rats

exposed to 144μg/kg. by injection. Taken together, these studies strongly suggest that Gulf War syndrome is an effect of inhalation of micrograms of Uranium and draw attention to the extraordinary neurotoxicity of the material.

Table 6 Recent studies of neurological effects of Uranium

Study	**Results**
Monleau *et al* 2005 IRSN, France	Inhalation of Uranium by rats. Uranium concentration in brain: Olfactory bulb> hippocampus> frontal cortex> cerebellum. Behavioural changes shown
Barillet *et al* 2007 IRSN, France	Oxidative stress and neurotoxicity in adult male zebrafish exposed to U-238 and U-233 in water. Oxidative stress and neurophysiological changes (increase in ACh) in exposures to both isotopes
Pellmar *et al* 1999	Depleted Uranium fragments implanted in rats and caused electrophysiological changes in hippocampal slices
McDiarmid *et al* 1999	Gulf war veterans studied found subtle effects on reproductive and central nervous system function
Briner and Murray 2005	Rats exposed to drinking water containing 75 or 150mg/l DU. Behavioural changes after 2 weeks; increased lipid oxidation
Lestaeval *et al* 2005 IRSN France	The brain is a target organ after depleted Uranium exposure. 144μg/kg injection in rats caused at kidney levels of 2.6 μg/g. This level would be normally seen as a sub toxic dose to the kidney. However, this was associated with decrease in food intake and sleep wake cycle disturbance.
Barber *et al* 2005	Short term kinetics of Uranium in rat brain after intraperitoneal injection 1μg/g animal. Uranium entered the brain rapidly and was initially concentrated in the hippocampus and striatum. Clearance was slow; contents of hippocampus, cerebellum and cortex was still high after 7 days

4 Animal studies, cell cultures and mechanisms

The ICRP-based desk analyses (Royal Society, WHO, SHER, RAND, ATSDR etc.) which employ absorbed dose and use risk factors for cancer culled from the Japanese A-Bomb cohorts do not predict the observations and must now be abandoned. Clearly Uranium exposure is much more hazardous. Cell culture and animal experiments have provided useful information for developing and understanding of the mechanism involved. What all these studies seem to show, is that internal Uranium exposure, to particles but also to ionic forms, seems to be acting as if it were considerably more radioactive than it is on the basis of its intrinsic radioactivity. Thus U-238 exposure causes oxidative stress, genomic instability, chromosome damage, micronuclei formation, all consequences of ionizing radiation exposure, yet in

some experiments the concentration is so low that there is stochastically no radiation exposure because there are too few decays. This finding has been variously interpreted as suggesting a chemical mutagenic effect, a heavy metal effect, or a synergy between radiation and chemistry. Of course, one re-discovery is the affinity of Uranium for DNA phosphate. The affinity of the uranyl ion, UO_2^{++} for Calcium Ca^{++} sites was known in the 1960s when the substance began to be employed as an electron microscope stain. The affinity constant was measured in an elegant flow experiment by Nielsen *et al* in 1992 and was of the order of $10^{10}M^{-1}$. This would suggest, in mass-action equilibrium terms, that at quite low concentrations (100ng/l) there is a significant amount of Uranium bound to the phosphate backbone of the DNA. This seems to agree with the experimental observations of biological effects reviewed here. The ECRR model is particularly concerned with radionuclides which bind to DNA (Strontium-90, Barium-140) since these beta emitters decay into the DNA and also change their charge and transmute into a radioactive daughter producing an ion and perhaps Auger electrons. The charge change alone will cause an ionization on the DNA. It seems that Uranium is therefore in this category, which would result in a weighting (see Chapter 6).

But there is also the fact that Uranium has a high atomic number and would therefore amplify natural background gamma radiation (and also the photon radiation which it, itself, produces, in addition to any photon radiation from other Uranium isotopes present in any mixture. The conclusion of the Committee is that such a mechanism is capable *on its own* of explaining the many anomalous findings reviewed in this chapter and in this section. The extent of the enhancement must await experimental investigation, but these experiments are straightforward, involving simultaneous exposure to Uranium and to X-rays of various energies. The use of dilute uranyl salts as an enhancing agent for X-ray targeted radiotherapy for cancer was suggested in a British Patent Application in 2007 (Busby 2008). It is clear from the studies that significant binding in vitro occurs at 200μM or 84ng/l. This concentration is not currently considered toxic but is in the same range as that found in many drinking waters and in the urine of Gulf veterans.

A list of some studies which bear on the issue of the mechanism for the anomalous enhancement of Uranium both as ionic and as particulate is given in Table 7.

Table 7. Studies of Uranium effects in cell culture and in animals which reveal information on possible mechanisms for its anomalous hazard.

Study	**Result**
Gueguen *et al* 2007	Drug metabolism is altered following exposure of DU to rats; induces expression of CYP enzymes
Miller *et al* 2005	Leukemic transformation of haematopoietic cells in mice internally exposed to DU pellets.
Miller *et al* 1998	Transformation of human osteoblast cells to tumorigenic type after exposure to DU; 0.0014% cells were hit by alpha particles. Suggests no radiation effect.
Miller *et al* 2002	Showed both Uranium and tungsten capable of causing micronuclei in human osteoblast system and tumorigenic transformations.
Yang *et al* 2002	Malignant transformation of human bronchial epithelial cell by exposure to Uranium; DU shows carcinogenesis *in vitro*
Kalinich *et al* 2002	Depleted Uranium induces apoptosis in mouse macrophages
Gueguen *et al* 2006	Hepatic effects of Uranium on liver metabolism enzymes
Pariyakaruppan *et al* 2006	Uranium causes oxidative stress in lung epithelial cells
Grignard *et al* 2008	Contamination with depleted or enriched Uranium differently affects steroid metabolism in rats
Tissandie *et al* 2006	Short term DU exposure affects vitamin D metabolism in rats
Yazzie *et al* 2003	Uranyl acetate causes DNA single strand breaks *in vitro* in the presence of ascorbate. Suggests that affinity for DNA is greater than affinity for ascorbate.
Busby 2005a	Suggests and attempts to quantify secondary photoelectron effect for Uranium bound to DNA phosphate. Draws attention to affinity of Uranyl for DNA.
Busby 2005b	As above for Uranium particles
Stearns *et al* 2005	Induction of hprt mutations and DNA adducts in Chinese Hamster ovary cells at 200 μM (80ng/l).
Busby and Schnug 2008	Discusses SPE for Uranium in ionic form as explanation for observed effects
Elsaesser *et al* 2007	Monte Carlo simulations of Uranium, Gold and water nanoparticles of different sizes confirm the enhancements due to SPE
Wan *et al* 2006	In vitro immune toxicity of depleted Uranium: effects on mouse macrophages. At 50 and 100μM. Macrophage activity altered at 200μM for 2 h.
Pattison *et al* 2008	Monte Carlo simulation of Uranium particles in tissue confirm SPE effect is 'significant' but lower than suggested by Busby.
Hahn *et al* 2002	Implanted DU fragments cause soft tissue sarcomas in the muscles of rats.
Darolles *et al* 2010	Different toxicological profiles of depleted and enriched uranium: U235 causes chromosome aberrations (alpha) U238 causes aneuploidy (photoelectron toxicity explains this spectrum)

5 Conclusions

It is necessary to conclude that Uranium represents a perfect example of the problem resulting from the physics-based approach to radiation risk which ECRR2003 drew attention to. When doses are calculated in terms of absorbed dose following ICRP, the quantities of Uranium usually found in the environment confer very small doses compared with natural background gamma radiation, and even smaller when compared with the levels of dose which correlated with cancer in the A-Bomb groups. But it is clear that this approach is massively in error, since it has avoided or, more accurately, knows nothing about, chemistry, biology, physiology and pharmacology. These sciences were historically considered of less importance than physics and mathematics, in some deeply felt (by the physicists anyway) philosophical and emotional way. This is the flaw in rational analysis: it is only as good as its data, and if, in order to solve a problem, it has to be reduced to the level where a solution can be claimed, the answer is often wrong.

The Committee has had to deal with this very real problem by presenting a real solution; in this case the solution is to weight Uranium exposures by a factor of 1000 at normal background gamma photon levels (100nGy/h). This will be modified when experimental results of Secondary Photoelectron effects become available. It is clear that the effects of Uranium are wide ranging, and so to consider only genetic effects from Uranium exposure would be quite wrong. In addition, different types of exposure will cause different spectra of conditions.

In the case of conventional estimates of risk from internal Uranium, which essentially compare it with external doses, the errors are arguably greater than for any other material. There is now sufficient evidence to treat Uranium aerosols as if they had infinite biological effectiveness. The Committee therefore believes that using a risk factor to assess causality in Uranium-exposed populations or individuals should be done with extreme caution, even if that risk factor has been modified by application of a weighting that approximates observation.. If a disease or condition or genetic heritable effect of any kind is seen to increase after exposure to Uranium, causality should not be ruled out whatever the dose differential between a population before and after the exposure, or between exposed populations relative to unexposed controls.

The dose coefficients for uranium exposures are given in Table 8 below.

Table 8. Dose coefficients for uranium weapons exposures (from ECRR2010)

Isotope (form)	**Half life**	**ak(0-1) Sv/Bq**	**k(1-14) Sv/Bq**	**k(adult) Sv/Bq**
U-238 inhalation	4.5 E+9	2.5 E-3	1.2 E-3	8.4 E-4
U-238 μ particle	4.5 E+9	2.5 E-2	1.2 E-2	8.4 E-3
U-238 ingestion	4.5 E+9	2.5E-4	1.2E-4	8.4E-5

The committee believes to employ a risk factor, even one elevated by the weighting, to attempt to assess causality in uranium exposed populations or individuals should be done with extreme caution. There is now sufficient evidence to treat uranium aerosols as if they had *infinite biological effectiveness* since a single nanoparticle, if trapped in a biological replicating system may cause genomic amplification of damage over time. If a disease or condition or genetic heritable effect of any kind is elevated after exposure to uranium, or in those exposed to uranium relative to unexposed controls, causality should not be ruled out whatever the differential dose.

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