THE HEALTH RISKS FROM EXPOSURE TO URANIUM: ADVANCED BIOCHEMICAL AND BIOPHYSICAL ASPECTS

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1. The puzzling genotoxicity of Uranium

Following renewed interest in uranium toxicity generated by the military use of uranium weapons, it is found that the element exhibits genomic and other harmful effects not predicted by its radioactivity (e.g. Abu Quare and Abou Donia 2002, Craft *et al* 2004, IRSN 2005, Bertell, 2006). This has resulted in two schools of thought: those based on the conventional radiobiological risk assessments (e.g. Royal Society 2001, Wakeford 2001) and those pointing out that there are real genomic effects which cannot be explained or predicted (Baverstock 2005, Bertell 2006). There certainly seem to be experiments which show anomalous genomic or genetic effects (including Bosque *et al* 1993, Miller *et al* 1998-2005, Coryell and Stearns 2006,) but these are usually interpreted as implying some unelaborated 'heavy metal' effect for uranium. Historically, Uranium has been considered both a radiological and also a 'heavy metal' poison, following Calcium in its distribution within the body, i.e. building up in bone, and with the principle target for toxicity being the lung and the kidney (RS 2001). More recently, it has been shown that Uranium also targets the brain (ENVIRHOM 2006). Perhaps because the element is fairly common (and therefore assuming that natural = safe) the US EPA exposure limits in drinking water are as high as 20mg/l, whilst for inhalation the US NIOSH/OSHA give limits for inhalation of dust of 0.05mg m^{-3} , the US NRC giving 0.2mg m^{-3} (compare the German (BbodSchV) limit of 0.25mg m^{-3}).

Uranium has three common isotopes, U-238, U-235 and U-234. The natural U238/U235 isotopic ratio is about 138: 1. With specific activity of about 14 MBq/kg Uranium has been considered to be a low cancer risk. U-238, the main isotope has specific activity of about 12.4 MBq/kg so a concentration of 20mg/l represents 0.25Bq/l. but even counting the two beta-emitting daughter isotopes which are in equilibrium, the activity is still less than 1Bq/l. Uranium can have fast, medium and slow biokinetic clearance depending on the form: the slow components can remain in the body for a considerable time. ICRP68 gives dose coefficients for inhalation of Fast Medium and Slow dissolving forms of Uranium at 4.4 E-7; M: 2.6E-6; S: 7.3E-6 Sieverts per Becquerel respectively and for ingestion, the ICRP68 dose coefficients are generally 4.4E-8 and for the insoluble oxide UO2: 7.6E-9. On the basis of these figures, and because of a low transfer coefficient, routine ingestion of water at the high end of the EPA limit should not result in doses greater than some tens of microSieverts. The Royal Society (2001) calculated that that a continuous daily contamination by 1mg will eventually result in a steady-state kidney concentration of 12mg/l. Since this results in microSieverts, the Royal Society and World Health Organisation (WHO) dismissed the concerns of the Gulf War veterans who suffered from Gulf War Syndrome.

There are, of course, some fundamental problems with the IRCP radiological risk methods (see ECRR2003, CERRIE 2004, IRSN 2006): the assumption that absorbed dose (energy per unit mass) is an accurate measure of risk is arguable. The decays from particulate uranium, the type resulting from weapons use, are short range and doses near micron sized particles can be large for local tissue volumes within range of the decay.

Nevertheless it is not only exposures to particles that seem to result in health problems: uranyl ion also exhibits anomalous genotoxic effects at low concentrations causing genomic and genetic damage in cell cultures at concentrations where there are no significant alpha emissions (Miller et al 2002). Uranium (and also tungsten) particles cause genetic changes in cell culture elements and cause cancer in laboratory animals (Miller et al 2001). Uranium causes anomalous inflammation in lung, kidney, brain and other living tissue in rats and produces neurological effects in mice (ENVIRHOM 2006). Uranium causes chromosome damage in miners and Gulf War Veterans (French researchers, Zaire et al (1998), Schroeder et al (2003). How is this?

Since the 'absorbed dose' due to radioactive decay of uranium is very low in these studies, and in one experiment stochastically absent, these effects are puzzling on basis of conventional radiological risk models. They have been ascribed therefore variously to 'heavy metal toxicity' or 'chemical effects' or some unelaborated 'synergy between radiation and chemistry'. But what are chemical 'heavy metal' effects in the cell? Some proposed mechanisms from the literature include:

1. Enzyme poisoning by binding to S-H groups inhibits a critical reaction (e.g. Pb, Hg, Cd).
2. Binding to DNA phosphate (Mg^{++}, Ca^{++}, Sr^{++}, Ba^{++}, UO_2^{++}) deforms the DNA tertiary conformation and alters folding or unfolding in some way.
3. Binding to some critical 'receptors' antagonise normal binding by agonists (e.g. zinc finger proteins and DNA replication).
4. Inflammatory responses at tissue level (brain, intestine, kidney, lung). This mechanism is often described as 'Oxidative Stress' or 'Genotoxicity' since the effects are similar to effects with hydrogen peroxide and are alleviated by antioxidants and anti- free radical enzymes (e.g. superoxide dismutase) and/or various other markers and end points (e.g. ENVIRHOM 2005). But why?

In further examining this puzzle, let us consider what heavy metals have in common chemically. 'Heavy metals' have different valency states, affinity, redox equilibria, normal ionisation states, reactivity, Lewis acidity, ionic radii, energy levels, colour of compounds, work functions, solubility, melting points, boiling points, etc. etc. No physical chemist would understand the concept of a 'heavy metal'.

2. Secondary Photoelectrons

I will suggest here an explanation for these anomalies involving the idea that contamination by elements of high atomic number Z which have significant affinity for DNA will result in anomalously high absorption of natural background radiation by the DNA and its re-emission as photoelectrons. This represents a kind of focusing of natural background radiation (and any other external gamma or X-rays) into the DNA.

Chromosomal DNA is widely believed to be the the target for ionising radiobiological effects (e.g. see BEIR V 1990, ECRR2003, CERRIE 2004a, 2004b). It has been known for some time that Uranium binds strongly to DNA phosphate (DNAP)

as uranyl ion UO_2^{++} (Zobel and Beer 1961, Huxley and Zubay 1961, Constaninescu *et al* 1974, Nielsen *et al,* 1992). The affinity constant determined by Nielsen *et al* was of the order of 10^{10} M^{-1} at pH values below 5 with binding of one uranyl ion to every two phosphate groups. This would give half saturation of DNAP at concentrations of uranyl of about 10^{-10} M, which represents a cell concentration of 23ng/litre, at the lower end of urine concentrations that have been reported in those exposed to uranium weapons (Durakovic 2002, DUOB 2007). At higher pH's the amount of uranyl significantly increases to two ions per phosphate although the affinity constant decreased due to competition with polynuclear complexation reactions. Nielsen et al showed that the uranyl binding to DNA was greater than that of the powerful bidentate chelating agent citrate. The authors employed their discovery that uranyl ion induces photochemical single strand breakage in the DNA following irradiation with visible light (λ 420nm), a photoelectron-produced DNA lesion like those I am drawing attention to here, though at lower photon energy.

It is an interesting and well known fact that the absorption of gamma and X-rays increases rapidly with atomic number. Uranium (Z=92) and Lead (Z = 82) are thus employed for shielding purposes. The relationship is often assumed to approximate a fourth power one, though the exponent varies in the range 4.0 to 4.8 depending on gamma energy and element (Krane 1988). I can therefore compare the absorption of external photon radiation by uranium with that of calcium ions, those displaced by the uranyl from the phosphate DNA backbone. For water (Z_{eff} = 3.33) the fourth power ratio is greater than 500,000; for DNAP (Z_{eff} = 5.5) it is greater than 50,000 but for Ca^{++} and UO_2^{++} the fourth power ratio is about 450. Thus Uranium on DNA absorbs 450 times the background gamma and photon ionizing radiation than Calcium. But of course, Ca (Z=20) already absorbs 1000 times more gamma radiation than water and some 154 times more than the DNAP complex. It would thus seem that the Calcium ion associated with the DNAP is the dominant absorber in the genetic material of the cell. This effect is entirely absent from any microdosimetric assessment of risk. I compare Z^4 enhancements of absorption for some tissue components in Table 1 where I have normalised the ratio to water. Calcium, Strontium and Barium (included) all bind to DNA but their toxicity increases sharply in the sequence $Ba^{++}>Sr^{++}>Ca^{++}$ as we would expect from these considerations.

The amount of energy deposited in different constituents of the DNA in a cell per Gray of radiation absorption has been calculated (Ward *et al* 1988, BEIR V 1990). The cell was assumed to contain 6pg of DNA of which 1.2pg was phosphate. I reproduce the BEIRV Table1-1 (p14) where these fundamental results are shown, as Table 2. The calculation takes no account of the atomic numbers (and hence the gamma absorption) of the DNA constituents: the fourth column, which I added, shows that Ward et al 1988 calculate that the energy deposited per pg is the same whether we are dealing with water (Z_{eff} =3.3) or phosphate (Z_{eff} = 9.4). If, at a cell concentration of about 10^{-10}M, the phosphate were half saturated with uranyl ions, at a stoichiometry of one UO_2^{++} to two phosphate groups we can easily calculate the mass of uranium on the DNA. It is 0.7pg and this represents about 12% of the DNA in the cell by mass. This soaking up of uranium by DNA was actually reported by Huxley and Zubay in 1961 who observed that purified DNA took up nearly its own dry weight of Uranyl acetate from a 2% fixing solution. They employed uranyl acetate as an electron microscope stain.

Material	Z	Z^4	$H_2O = 1$
H_2O	3.33	123	1.0
DNAP	5.5	915	7.4
Ca	20	0.15 E+6	1220
Sr	38	2.1 E+6	17073
Ba	56	9.8 E+6	79675
Au	79	38 E+6	308943
U	92	72 E+6	585365

Table 1 Fourth power of atomic number Z for some materials of interest compared with water.

We also know from experiments with Auger emitters bound to DNA (e.g.I-125) that DNA is the target for the effects of ionising radiation (Baverstock and Charlton 1988). BEIR V (1990) state this clearly and tabulate results of calculations showing that the amount of energy deposited by one Gray of radiation in the DNAP of a cell is 36keV, of which 7.3keV were absorbed by the phosphate (see Table 2). This leads to 600 (60eV) ionisation events in the DNAP (BEIRV 1990) per Gray. The total absorption of external gamma radiation by uranium contaminated DNAP will therefore include the enhanced contribution from the uranium on the phosphate which is simply 7.3 x 450 = 3285keV per Gray resulting in an overall enhancement of deposition of energy by a factor of almost 100-fold.

Constituent	Mass per cell (pg)	eV deposited	*eV per pg*
Deoxyribose	2.3	14000	*6086*
Bases	2.4	14700	*6125*
Phosphate	1.2	7300	*6083*
Bound water	3.1	19000	*6129*
Inner hydration	4.2	25000	*5952*

Table 2. Amount of energy deposited in DNA per cell per Gray according to Table 1-1 of BEIRV 1990 and based on Ward et al 1988 with column showing that BEIRV made no allowance for the gamma cross section of the various atoms.

Thus, for an annual absorbed dose of 1mSv, the DNA of tissue containing quite modest and environmentally common levels of uranium would be 100mSv. For those who are occupationally exposed, the enhancement would probably be greater both through the internal uranium concentration term and also the external gamma radiation term. Perhaps it is this overlooked phantom radiotoxicity resulting from photoelectron effects that explains the various anomalous findings referred to earlier. The gamma radiation is absorbed preferentially by the Uranium atoms: the absorption cross section for gamma photons is some 500,000 times greater than that of water. But this does not mean that all the energy from the absorption is deposited in the DNA, since the photoelectrons may have various energies, ranges and track directions.

But it is not only photoelectrons that are the ionizing agent near the DNA. Photo emissions include electrons with a spread of ranges and velocities proportionate to

the incident photon energy. But there is also ionization of the uranium atom itself with 'catalytic' local effects. The loss of an electron will ionize the uranium and produce an excited or 'hot' species which may lose energy by abstracting an electron from local hydration water or some other local molecule (see e.g. Gracheva and Korolev 1980). This will lead to at least one production of a different reactive hot radical or ionic species at the Uranium site, and note that the effect is catalytic, that the Uranium is regenerated.

As far as the emitted photoelectrons electrons are concerned, for condensed phase DNAP in dividing cells, they will have a high probability of damaging DNAP along their track only where this track intercepts or lies near the DNAP. To assess the likelihood of DNA interception, that is the production of ion pairs close enough to the DNA for damage to occur, we need to examine the spectrum of ranges and thus energies. The energy dispersion of environmental gamma radiation at any point in tissue is a consequence of many energy splitting processes (Compton effect, pair production, Bremsstrahlung, etc.) with the result that the event number (ionization events, counts) increases rapidly with decreasing photon energy. This means that at the DNA, especially deep within the body of human beings (though not, perhaps to such an extent within small animals like mice and rats) there will be the highest density (counts, events) of photoelectrons of low energy and short path length. It will be these that create the highest number of ionizations close to, or inside the DNA. Thus far I have addressed ionic high Z elements bound to DNAP. But what of particles of high Z materials incorporated within tissue?

3. Respirable uranium particles

The analyses by the Royal Society were directed at respirable uranium oxide particles. Uranium weapons produce large quantities of uranium oxide aerosol particles of diameters less than 1μm which are widely dispersed, long lived, and respirable (RS 2001, 2002). Their effects remain in question (Busby and Hooper 2007). Research has shown that uranium particles can indeed cause anomalous genotoxic and other harmful effects (Miller et al 2001 , Monleau et al 2006) and again, the conclusion have been that the material displays some 'chemical heavy metal ' or 'nanoparticle' effect. What is overlooked is photoelectron enhancement. Gamma photons induce photoelectrons in high Z particles, but since high Z materials also have high stopping power for electrons, the range of the photoelectron in the material now becomes a dominant consideration. The variation of photon penetration into the particle with photon energy is also important. For example, the penetration of a 20keV photon into uranium oxide is 0.0015 cms but at 50keV the penetration is 120 cms (see Krane 1988). I have made approximate calculations based on the photon and electron attenuation coefficients of uranium oxide particles of different diameters elsewhere (Busby 2006) and these suggest that the photoelectric enhancement of incident gamma radiation is only significant for particles of diameter less than about 5μ diameter. For larger particles, photoelectrons excited within the mass of the particle do not emerge. The result for small particles of high Z elements is that there will be an enhanced short range photoelectron ionization field close to the particle. The high Z particles whether intrinsically radioactive or not will behave as 'hot particles' but without any radiological decay. The effect will be largely irrelevant for large pieces of shrapnel, for metal prostheses made of gold, gold tooth

fillings and so forth, but may be important for other exposures (e.g. platinum particles from catalysers).

4. Supporting evidence, conclusions and speculations

These photoelectron enhancement effects have been reported (Herold *et al,* 2000), and for gold nanoparticles have been employed (Hainfeld *et al* 2005), and even patented (US Patent 6955639B2), for enhancing radiotherapy. The enhancement of ionization by elements of high atomic number was considered as early as 1949 when Speirs showed that there would be a ten- fold enhancement in tissue near bone due to the calcium in the bone. Since then a number of groups have looked at the effect including Regulla *et al* 1998 who actually measured photoelectron enhancements of 100- fold near thin gold foils. The process has serious implications since one other piece of supporting data may be the discovery of tungsten particles (Z = 74) in the atmosphere of Fallon, Nevada where there is a much discussed childhood leukaemia cluster (Sheppard *et al* 2007). Kalinich *et al*, 2005 actually succeeded in inducing cancer in rats in which tungsten particles had been embedded. There are also large amounts of uranium (mainly particulate and sub micron oxides) in the Irish Sea sediments and these would be available by inhalation following sea to land transfer. The uranium contribution to analyses by the various UK committees examining child leukemia near Sellafield has not allowed for any photoelectron enhancement exposures and indeed treated the uranium exposures to the lymphatic system of children as some 'natural' exposure which could be used to assess the likelihood that the anthropogenic contribution was less (discussed in CERRIE 2004).

The idea that uranium particles (or uranium atoms bound to DNA) amplify effects from external irradiation is amenable to experiment. We could examine the extent of Uranium binding to DNAP *in vivo* and also determine the range of photoelectrons arising from background radiation spectrum amplification. Finally, I have concentrated here on Uranium. But of course, this secondary photoelectron enhancement has wider implications for exposures to other high Z elements both as molecular or ionic species and as particles. It is an interesting fact that living systems generally employ few elements of atomic number above Chloride (Z = 17) and Calcium (Z = 20). The highest atomic number element existing in any quantity in mammals is Iron (Z = 26), and in general, no element above the first row Transition metals is employed by living systems with the unusual exception of Iodine (Z=53). For evolution to employ any of the many high Z elements available would carry a serious disadvantage on a planet with background gamma radiation. I also notice that the two most radiosensitive systems in mammals are the blood (leukemia) and the Thyroid gland (cancer). These two systems are the main depots of Iodine (Z=53) in the body. The unusual jump over Bromine to Iodine in the thyroid allows me to speculate that the up-regulation of genes driven by thyroid hormones may involve radiation repair i.e. that one function of the thyroid is as a biological radiation detector.

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