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Preamble

My name is Keith Frederick Baverstock. I graduated from London University with a BSc and PhD in Chemistry and undertook post graduate fellowships at AECL in Canada (NRC) and University of Nottingham in the UK (SRC) before joining the UK Medical Research Council at Harwell in 1971 with the dual remit of research and assisting in formulating Council's advice to government on the biological bases of effects on health of ionising radiation. In 1991 I joined the World Health Organisation (European Regional Office) to found and head up the radiological section of the European Centre of Environment and Health in Rome. In 1998 I became Regional Advisor for public health and ionising radiation at a dedicated project office in Helsinki, Finland and in 2002 I moved to the WHO European Centre for Environment and Health in Bonn Germany. I retired from WHO in May 2003 and am presently a Docent in the Department of Environmental Sciences at the University of Kuopio, Finland. In January 2007 I will take up the post of Professor of Health and Ionising Radiation at the University of Kuopio.

I have, therefore, extensive experience in advising on public and occupational health issues relating to environmental contaminants, specifically radioactive materials. Uranium is a radioactive element naturally distributed in the environment and present in water and foodstuffs. It would be toxic to humans if it were not for the fact that man has evolved in such a way as to largely exclude ingested uranium from incorporation into the bodily tissues. Uranium is naturally available in air only in very low concentrations and then only in an insoluble form. It probably results in a small carcinogenic risk. Depleted uranium is natural uranium depleted of the 235U, the fissionable isotope of uranium. DU is somewhat less radioactive than natural uranium but behaves identically in terms of its chemistry.

The case that I will make is that relevant evidence exists in the peer reviewed scientific literature to indicate that uranium is a genotoxic agent, i.e., that it is capable of damaging the genetic material of humans and potentially leading to cancer.

The evidence

It is widely accepted that uranium, inhaled as insoluble particles, is carcinogenic to the lung through its radioactive emissions and that if soluble will cross the blood /air barrier of the lung to become systemic and be physiologically toxic to the kidney.

The international body responsible for categorising agents according to their carcinogenicity is the International Agency for Cancer Research (IARC) which, with the assistance of expert groups, produces *Monographs* on the carcinogenicity of specific agents. In 1999 IARC investigated surgical implants and other foreign bodies, including depleted uranium fragments, but concluded that in this context DU should be regarded as a Group III agent (not classifiable as carcinogenic to humans)

but it has categorised alpha emitting radionuclides collectively as Group I agents (i.e., as carcinogenic to humans).

However, I maintain that the evidence supports the case that inhaled uranium is additionally potentially carcinogenic in a broader sense, specifically that if it becomes systemic (i.e., is in a soluble form) it has in addition genotoxic properties, not necessarily mediated by its radioactivity, which will be potentially carcinogenic in a number of tissues in addition to the lung.

In categorising agents for carcinogenicity IARC considers three categories of evidence, namely, that derived from:

- human epidemiology
- animal experimentation
- data on mechanisms of carcinogenesis

As far as I am aware there have been no serious studies (i.e. those with a realistic chance of confirming or rejecting a statistically significant increase in cancer[1]) on exposure to depleted uranium. The UK Royal Society has reviewed studies covering 120,000 workers in the uranium processing industry and found the studies inconclusive in that they did not eliminate the possibility of there being a carcinogenic risk although they did rule out a very large risk (*1*). It should be noted that most of the exposure in these applications did not involve soluble uranium.

There appear to be no long-term peer reviewed studies of uranium toxicity in animals with systemic uranium. There are, however, long term studies of natural uranium oxide (i.e. insoluble) inhalation (*2, 3*) which clearly indicate the carcinogenicity to the lung of this mode of exposure and possibly its involvement in non-Hodgkins lymphoma.

There is, however, a significant body of evidence that the exposure of cells *in vitro* and *in vivo* to uranium (mostly depleted uranium) does induce phenomena that are closely associated with the carcinogenic process. These include:

- Genomic instability (*4*) (a phenomenon observed *in vitro* and *in vivo* that mirrors the carcinogenic process)
- Transformation to a tumourogenic state (*5, 6*) (*7*) (*8*) (*9*) (affected cells when injected into mice grow as cancers)
- Induction of mutations (*10*) (*11*) (mutations characterise almost all cancers)
- The generation of oxidative damage to DNA (*12*)
- Activation of gene expression pathways (*13*)
- The induction of double strand breaks in DNA (*14*)
- Induction of chromosome aberrations (*15*) (*9*) (rearrangements of the genetic material within and between chromosomes are characteristic of cancers)
- Formation of DNA-U adducts (*11*)

Furthermore, a statistically significant increase in *hprt* mutations[2] in peripheral lymphocytes has been observed in three US first Gulf War veterans[3], with embedded

[1] Given the limited time that DU has been used in munitions it is likely that epidemiological studies today would be insufficiently sensitive to detect effects in exposed groups.

[2] The identity of the gene is not particularly relevant here as there are only a limited number of genes that can be measured in this way; it is rather the fact that a mutation can be observed in lymphocytes, cells which derive from bone marrow stem cells. The mutation was most probably induced in maturing

DU fragments related to their DU burden as reflected in measurements of uranium in urine (*10*). Other results indicate that repeated exposures through inhalation tend to potentiate the genotoxic effects (*16*).

The chromosome aberration observations on open pit uranium miners in Namibia (*15*) are also highly relevant as human evidence[4]. However, a paper published in 2001 claims to have repeated the identical chromosome analyses on mineworkers from Namibia and found no effect (*17*). However, the authors of the 1996 paper (*15*) apparently have not retracted their claim. Both papers include authors who are highly experienced scientists who have been working in the field of chromosome analysis for decades. One of the authors of the 1996 paper (JRK Savage) is an author of a "state of the art" review of chromosome aberration formation (*18*) and the 1996 paper is cited in this review, which was submitted for publication in November 2001, some 4 to 5 months after the 2001 paper appeared in print. As elevated frequencies of chromosome aberrations in peripheral lymphocytes are associated with an elevated risk of cancer (*18*) this is an important question to be resolved.

In addition some of the studies showing effects were carried out in parallel with exposures of the same experimental system to the element nickel (e.g. (*4*) (*8*) (*13*)) demonstrating a comparable degree of effect for DU and nickel which IARC has designated as a Group I agent (i.e. carcinogenic to humans). Uranium shares the "heavy metal" character of nickel, both avidly binding to DNA and proteins in the cellular environment.

The genotoxic character of uranium is not addressed by the WHO Monograph (*19*) and receives only a passing mention in the Royal Society Reports (*1, 20*). Both agencies concentrate on the radio-toxicity to the lung from insoluble uranium and the physiological toxicity to the kidney from systemic uranium.

The depleted uranium oxide dust produced when DU munitions burn has no natural, or indeed historical, analogue as it is composed to two oxides, one insoluble the other sparingly soluble and is produced in particle size distributions not typical of particles normally encountered in radiological protection. There is, therefore, much uncertainty about how these particles will behave in the environment and when inhaled and this is reflected in the Royal Society reports (*1, 20*). As there is a soluble component inhalation of particles would be expected to lead to a systemic burden of uranium and the bias towards small particle sizes would be expected to lead to penetration of the deep lung where clearance processes are slow. Some evidence suggests that very small particles could cross the lung/air barrier, a possibility not so far examined in any detail.

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bone marrow cells (15) but other possible sites include thymus and circulating lymphocytes. It is, therefore, a significant indication that a mutagenic agent is operating.

[3] There are a total of 39 subjects with embedded DU fragments with uranium in urine concentrations ranging over 5 orders of magnitude. The frequency of *hprt* mutations shows an association with uranium concentration in urine which is significant and the three individuals with the highest uranium in urine concentrations show the highest mutation frequencies. The authors conclude "These findings are consistent with a mutagenic effect of depleted uranium, at least in the cases with retained body burdens."

[4] 11 non-smoking miners with at least 12 years of history working in the mine or the associated milling facility were compared with controls living at least 12 miles from the facility. The aberrations were observed in circulating lymphocytes suggesting they were most probably induced in maturing bone marrow cells. A comparison of miners with non-smoking controls showed a highly significant excess of aberrations in the miners ($p < 0.00001$). The authors conclude that the miners are at a risk of acquiring increased genetic damage, "which may be associated with an increased risk of malignant transformation."

Conclusions

It has, therefore, to be concluded that DU oxide dust dispersed to the environment presents a number of potential risks to the health of populations in the vicinity primarily through the inhalation of resuspended particles:

1. A radiotoxic risk to the lung from the insoluble components
2. A genotoxic risk to the lung from both the soluble and insoluble components
3. A genotoxic risk to other tissues in the body from the soluble component crossing the blood/air barrier
4. A physiological toxicity to the kidney and possibly other tissues, from systemic uranium

Only risks 1 and 4 have been examined in detail in the currently available risk assessments (*1, 19, 20*) for DU.

The Royal Society reports (*1, 20*) emphasise the considerable uncertainties in making risk assessments for exposure to DU (mainly in the military context) because of:

- Lack of knowledge of the extent of likely intakes
- The lack of adequate long-term studies of uranium toxicity.

The same considerations apply to the public health implications for populations living on former battle sites. This is particularly so where the climate is dry and arid as it may take some considerable time before weathering of the DU oxide dust particles leaches away the soluble component and/or the particles become unavailable for resuspension.

Without direct evidence in either humans or animals IARC would be unlikely to classify an agent under Group I, but if there were strong mechanistic evidence and the agent in question is a member of a group for which there were Group I or IIA classifications then they could assign the agent to Group IIA (indicating that it was probably carcinogenic to humans). It could be argued that uranium is a heavy metal and nickel, another heavy metal, behaves in a mechanistically similar way, thus indicating Group IIA for uranium. A similar argument can be applied concerning radiation, another Group I agent. By any standard the mechanistic evidence would now warrant classification at least as Group IIB (possibly carcinogenic to humans). IARC's opinion would be likely to be influenced towards Group IIA classification by the evidence from first Gulf War veterans with embedded DU fragments who exhibit an excess of *hprt* mutations related to their DU burden (*10*), by the evidence from the Namibian miners (*15*) (if that evidence proves to be sound) and the fact that many of the *in vitro* experimental systems exhibiting effects use cells of human origin.

In 2000 the European Commission clarified its position on the precautionary principle. It stated[5]:

[5] See: http://ec.europa.eu/dgs/health_consumer/library/pub/pub07_en.pdf

Recourse to the precautionary principle presupposes that potentially dangerous effects deriving from a phenomenon, product or process have been identified, and that scientific evaluation does not allow the risk to be determined with sufficient certainty.

This seems to me to encapsulate the position we are faced with as far as the health impact of exposure to DU oxide dusts are concerned. Others are better qualified than I am to recommend what would be a "proportionate" measure, however, cleanup of existing sites and a moratorium on further use until the position on risk to human health is clear, certainly would not be disproportionate. However, the Commission does make two recommendations which I am qualified to comment upon, namely that there should be periodic scientific review and that responsibility should be assigned for producing the scientific evidence for more comprehensive risk assessments.

I think it is clear that the major risk assessments of the health impact of DU (*1, 19, 20*) have not addressed the genotoxic hazard and it is conspicuously absent from much cited assessments of toxicity such as that by Priest (*21*). It is also the case, as far as I am aware, that no specific body has been assigned the responsibility to produce the necessary evidence that DU oxide dusts do not pose a hazard to health.

Disclaimer

To the best of my knowledge the above is a faithful and true account of my professional assessment of the evidence relating to the potential toxicity of depleted uranium oxide dusts. It is not a comprehensive account as the situation is changing with new evidence appearing and I have not had the opportunity to carry out a comprehensive analysis of the latest evidence. I have not to my knowledge omitted any evidence that contradicts the main thrust of the above, namely that uranium is potentially genotoxic and therefore probably a carcinogen.

K F Baverstock
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