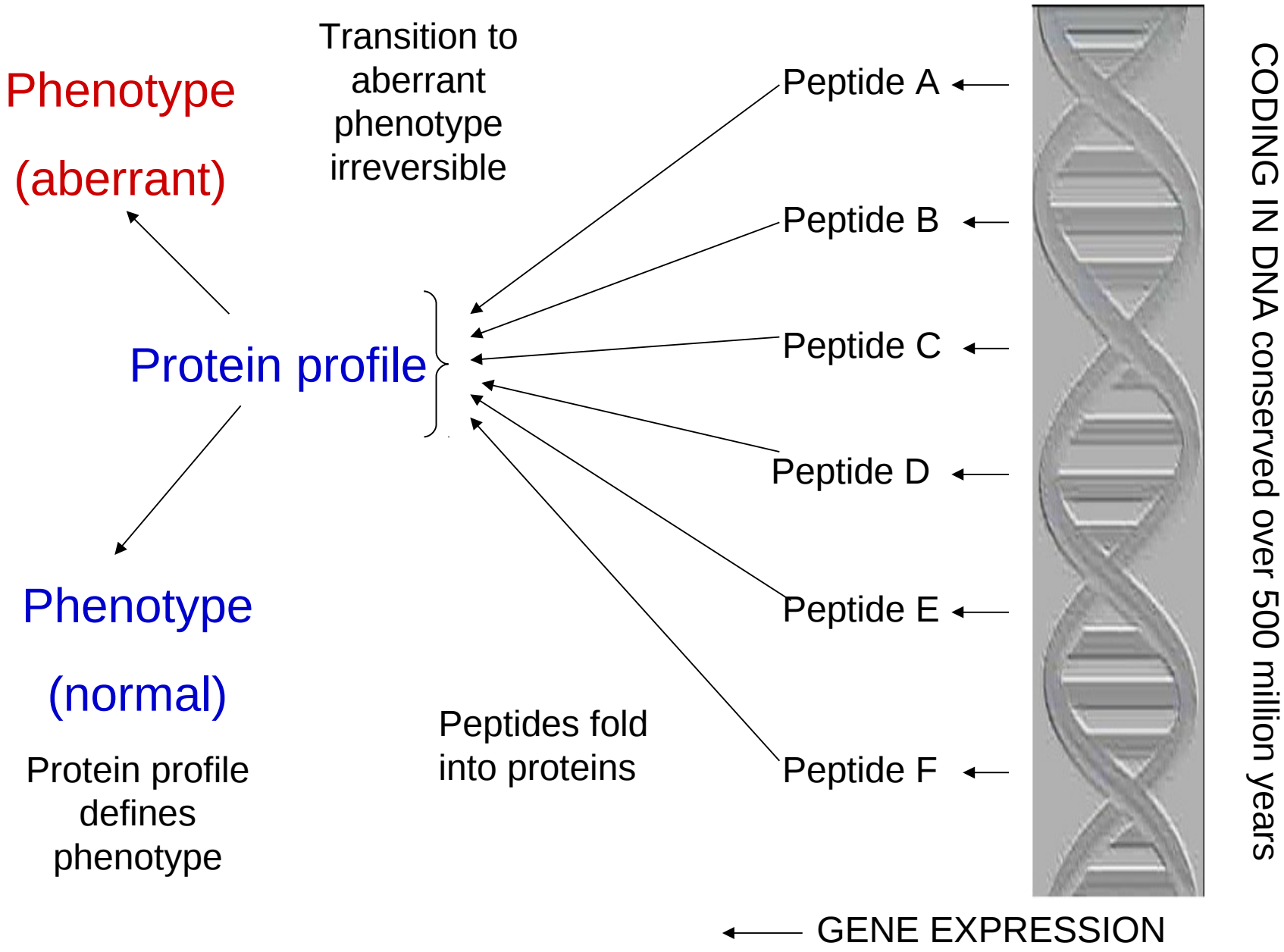
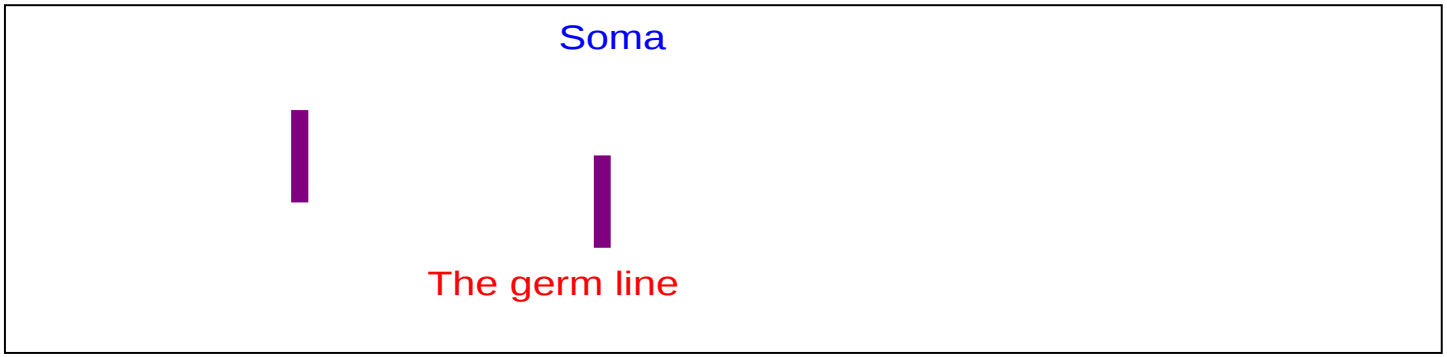
The toxicity of depleted uranium

Keith Baverstock

University of Eastern Finland


Phenotype
(aberrant)
Transition to aberrant phenotype irreversible
Peptide A
Peptide B
Peptide C
Peptide D
Peptide E
Peptide F
Protein profile
Phenotype
(normal)
Protein profile defines phenotype
Peptides fold into proteins
CODING IN DNA conserved over 500 million years
GENE EXPRESSION

Human cells fall into two categories, germ and somatic.



Typically a human cell uses a profile of some 3,000 proteins (there are about 100,000 in total) and there are more than 200 terminally differentiated somatic phenotypes with many more transitional phenotypes. But more important are a smaller number of stem cells that generate terminally differentiated cells.

Phenotypic modification of the germline can result in health detriment in all subsequent soma.

A typical somatic cell performs hundreds of function many largely invisible, including communications with other cells in the tissue to which it belongs. The cell's natural tendency is to proliferate but in a tissue the cell is constrained by signalling from other cells. Cancer can be seen as unrestrained proliferation.

Terminology:

Harm: a palpable health detriment

Hazard: a POTENTIAL risk of harm

Risk: the quantification of that harm.

Uranium is ubiquitous in the environment and when systemically incorporated into the body causes harm. It is thus a hazard.

If it is in such a form such that it can be incorporated systemically it presents a risk.

The dust that is generated by DU munitions is in such a form – it is partially soluble and therefore presents a risk. The magnitude of that risk may depend on circumstances.

What can DU do to DNA, Chromatin and the Cell?

DNA

Mutation

Strand breakage

Base damage

Cross-linking of strands

Chromatin

Dicentric chromosome aberrations

Cells

Modification of gene expression

Malignant transformation

Genomic instability

Damage to fertility

Transgenerational effects

International bodies are responsible for advising governments on the hazards of various agents:

1) Globally the World Health Organisation in Geneva evaluates the risks to health from toxic agents such as tobacco.
2) Globally the World Health Organisation's International Agency for Research on Cancer (IARC) identifies and categorises human carcinogens.
3) In Europe the Scientific Committee on Health and Environmental Risks (SCHER) advises the European Commission on hazards from chemicals in the environment more broadly than just cancer.

Both WHO and SCHER have given views on DU toxicity although IARC has not considered it specifically it has considered radiation as a carcinogen.

In 2001 the **WHO** (Geneva) published a monograph on Uranium with a special emphasis on DU. They considered both the radiological aspect and the chemical toxicity. However, in the latter case they focussed solely on the physiological toxicity to the kidney and purposefully rejected the possibility of a chemical genotoxic effect.

In terms of the radiological aspects they simply re-iterated the position of the International Commission on Radiological Protection (ICRP), calculating the radiation does to the lung assuming DU to be insoluble. As DU has a relatively low specific activity this dose is rather small and does not include the possibility of genotoxicity having the kinds of effects discussed earlier. ICRP dismisses soluble U as a problem for chemical toxicity, so the radiological risk from systemically incorporated DU is ignored.

When asked later why the evidence relating to genotoxicity was ignored the project manager stated that WHO needed firm evidence not fairy tales. We will come back to this shortly.

The **International Agency for Research on Cancer (IARC)** have developed a protocol for identifying carcinogenic agents.

IARC categories of human carcinogenicity

Group I	established human carcinogen
Group IIA	*probably* a human carcinogen
Group IIB	*possibly* a human carcinogen
Group III	not classifiable as a human carcinogen
Group IV	not a human carcinogen

In determining the carcinogenetic status for any given agent the highest priority is placed on human epidemiological evidence, then animal (*in vivo*) carcinogenicity studies, then human cells in culture and then animal cells in culture and finally mechanistic studies – strand breaks in DNA for example

All radioactive compounds (therefore including DU) are Group I carcinogens because radiation is a Group I carcinogen.

What does **SCHER*** have to say about genotoxicity and carcinogenicity?

Formally, a carcinogenic effect can only be assessed in experimental studies on animals or in epidemiological investigations. If valid studies of these types are not available or if studies have yielded limited information only, *in vitro* and *in vivo* approaches can provide some information on the likelihood that a given agent is carcinogenic. It should be realised, however, that these studies cannot give a definite answer to the question about a carcinogenic potential. Moreover, due to this inherent uncertainty and the use of surrogate endpoints, i.e. genotoxicity instead of carcinogenicity, they can be used for hazard identification but, so far, not for risk assessment (i.e. derivation of numbers).

In specific cases, agents may be regarded as potential genotoxic carcinogens on the basis of positive *in vivo* genotoxicity tests. Although the positive predictivity of most *in vivo* genotoxicity assays is limited, compounds shown to induce DNA strand breaks, chromosomal mutations and, particularly, unscheduled DNA synthesis or gene mutations *in vivo* in addition to positive *in vitro* data are highly suspect of being carcinogenic. These compounds may be considered potential carcinogens until results from appropriate repeated dose studies in animals or human data become available.

My evaluation to the European Parliament Committee on Defence of the SCHER report can be found on my website: http://www.kbaverstock.org

*SCHER is the advisory committee of the EC responsible for advising on the hazards of chemicals in the environment.

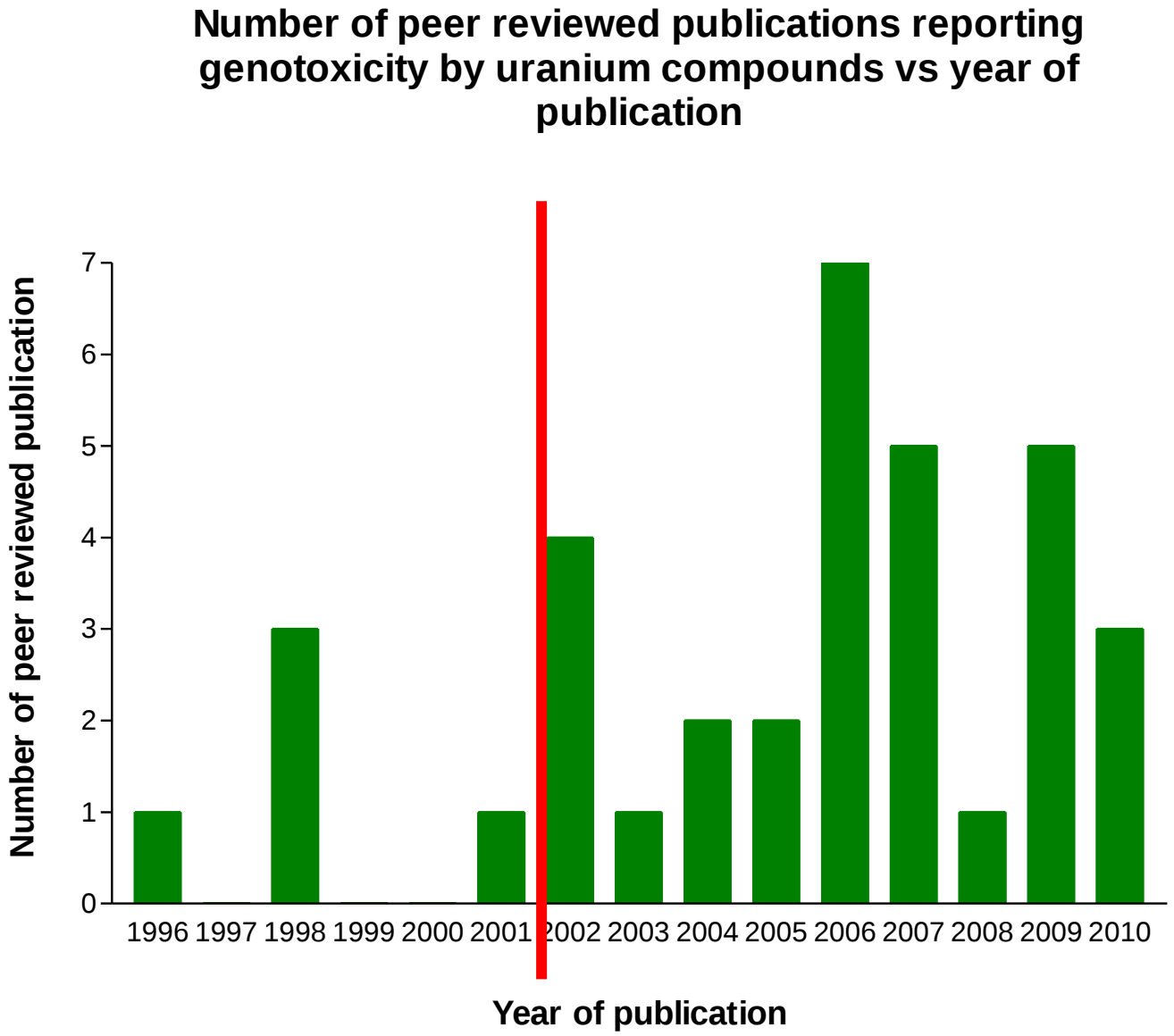
There is no human epidemiological evidence from a large exposed population from which definitive evidence of carcinogenicity can be derived – no such study as been done – lack of evidence does not mean lack of effect! One human population is under study, namely a group of some 80 veterans in the US with embedded DU fragments in their bodies. This group, as well as being small, is not systematically studied and the absence of effects reported cannot be taken seriously as evidence that DU has no health effects.

There are more than 15 papers reporting effects of DU in animals (mice and rats) ranging from carcinogenic potential to gene expression modification to hereditary and fertility effects to behavioural effects.

There are more than 10 papers reporting genotoxic effects in human cells in culture and 9 papers reporting effects in animal cells.

Some of these report increases in DNA strand breakage and mutation.

In spite of this evidence SCHER concluded that there was no risk to humans from DU dusts citing the fact that out of some 50 persons from the Balkans who had been measured for DU none apparently have any DU in their bodies.


Number of peer reviewed publications reporting genotoxicity by uranium compounds vs year of publication
Number of peer reviewed publication
0
1
2
3
4
5
6
7
1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010
Year of publication

Of especial concern are papers reporting modification of gene expression (unscheduled DNA expression). Damage to DNA may occur in places that have no impact on phenotype but phenotype is highly contingent on gene expression and so this is a much more concerning end-point.

Modification of phenotype is an irreversible process and as far as cancer is concerned it needs only to occur in a single cell for it to present a risk of disease.

Radiation and heavy metals are capable of inducing genomic instability, an irreversible effect (also observed in cells in culture exposed to DU), which is an abnormal phenotype capable of progressing into disease endpoints.

There can be little doubt that DU has a strong potential to cause disease if it is internalised into the body and it is established that DU oxide dust is capable of doing this for a period after its formation. The length of this period will depend on the environmental conditions to which it is exposed. In dry and arid climates this period could be months to years.

Conclusion:

DU dust from munitions is a clear HAZARD and because it can be systemically incorporated presents a RISK. How large that risk will be depends on the specific circumstances. In dry arid climates it could be considerable but where there is high rainfall it might be quite small and limited in duration.

Rate, molecular spectrum, and consequences of human mutation

Michael Lynch[1]

Department of Biology, Indiana University, Bloomington, IN 47405

This contribution is part of the special series of Inaugural Articles by members of the National Academy of Sciences elected in 2009.

Contributed by Michael Lynch, December 3, 2009 (sent for review September 13, 2009)

Quoted from the Conclusion

Thus, the preceding observations paint a rather stark picture. At least in highly industrialized societies, the impact of deleterious mutations is accumulating on a time scale that is approximately the same as that for scenarios associated with global warming—perhaps not of great concern over a span of one or two generations, but with very considerable consequences on time scales of tens of generations. Without a reduction in the germ-line transmission of deleterious mutations, the mean phenotypes of the residents of industrialized nations are likely to be rather different in just two or three centuries, with significant incapacitation at the morphological, physiological, and neurobiological levels.

THANK YOU FOR YOUR ATTENTION!