

Reviewer's report

Title: An Epidemiological Perspective on the Teratogenicity of Depleted Uranium Aerosols

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Reviewer: Dr. Michel Fernex

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1. The manuscript is of considerable general medical interest, as it analyzes the available epidemiological studies, to answer a controversial, but essential question: is Depleted Uranium (DU) teratogenic?

2. The experimental data considerably reinforce the epidemiological findings. A certainty on the subject, would require complementary epidemiological studies, especially among soldier families of the different countries involved in the Gulf Wars. The military authorities could contribute to such epidemiological studies, obtaining a high percentage of participants, in well defined comparative groups. The inquiries in the families would imply personal contacts, as self-reporting may be responsible for bias. The army may however have little interest to contribute to epidemiological studies on the risks associated with inhaled DU-aerosols, close to the battlefield.

3. The authors have taken an historical approach, from down-winders from DU-munition testing areas, to reports from the Gulf War. The most convincing large, well documented series, is based on the Basra (Iraq) register study, which shows on the one hand a constant number of births each year, between 1990 and 2001, with a transient drop in 1991, the year of the war (Table 1). On the other hand, the overall increase of congenital malformations by a factor more than four: multiple congenital malformations increased by a factor seven; this is important, as multiple malformations most often have a genetic origin or component. Congenital heart diseases increased by a factor eight. These data are based on a total of nearly 130'000 births (Table 2). The authors are very prudent, indicating the socio-economic problems encountered in the country. Malnutrition may have increased in infants and children, but restricted food during pregnancy, with some exceptions, is not associated with the different malformations observed in Basra.

The findings among children of veterans of different allied nations, deployed versus non-deployed, show an increased risk, especially for cardiac malformations. Large studies based on questionnaires sent out, or phone interviews, may have bias, the response rate being relatively low. Self-reporting in itself may be source of errors. The comparative epidemiological trial by Padmanabham et al. (2004)* in Kerala, involving 72'000 children living in areas with quite different background levels of thorium monazite in the soil, is a good demonstration of the efficiency of personalized direct contacts with the families, for confirming statistically significant increase of congenital malformations, taking into account consanguinity and other factors. The comparison of children of veterans conceived before, versus after the involvement in the Gulf War, is a good approach for assessing the role of the military campaign. However, it does not exclude other potential risks associated with a military involvement in Iraq.

The malformation rate in uranium mining areas has also been studied, although the problem is different from the contamination close to the battle-fields. The contamination among non-miner families does not contribute to assess the risk bound with inhaled „insoluble“ DU-oxide aerosols, which might be present in down-winders of military camps where these modern weapons are being tested.

I would suggest that the definition of DU be summarized at the end of the introduction: DU in bullets is nearly 100% pure U-238. The aerosols of microparticles of U-238 oxides, which are practically insoluble, are produced by the impact of bullets on hard targets, responsible for oxidation at high temperature. This is the ceramic form of DU. It is the subject of the present paper, and also the title. The formed ceramic micro-particles, mainly smaller than 1 μ , thus penetrating into the alveoli, appear to be source of complex human diseases, following the inhalations of smoke or of invisible dust containing microparticles of „insoluble“ U-238 oxides, the question raised being are they teratogenic?

The radio-toxicity and the chemical toxicity of Uranium, a heavy metal is not in the objective of this presentation, even if the shrapnel-exposed human are mentioned. Wounded American soldiers with "large" foreign bodies of pure U-238, have not the same risks as soldiers having inhaled ceramic DU-oxide particles. The heavy metal has a systemic chemical toxicity, bound with its solubility. These soldiers probably have also inhaled smoke or dust with ceramic DU microparticles. More soluble uranium may cause supplementary toxic damages to distant organs such as the kidney.

The many thousands of unexploded DU-bullets remaining on battle fields, may also be collected by children as a toy, or by adults as a trophy. When measuring the gamma radioactivity of a single bullet (from Kosovo), that children carry in their pockets, the CRIIRAD laboratory in Valence showed that within a day, the radioactive dose received by the carrier exceeds the admitted yearly dose-limit for gamma rays.

The local concentration of radioactivity around the microparticles of ceramic DU in the tissues is enormous and corresponds after a sufficient time to "hot spots", like those produced more rapidly by plutonium particles, the tissular damage being mainly due to alpha particles.

In the described models used for experimental teratology, the portal of entry of the uranium oxide particles is different than for human, and the duration of observation of the laboratory animals tested is of course shorter than in human. However, using Injections of such nanoparticles to mice, valid information on radio-toxicity may be collected. These models are useful for studying the teratogenicity of „insoluble“ DU particles.

4. Conclusion

This exhaustive paper is important, as the authors make very prudent and critical analysis of the reports and publications they collected. They summarize the methods used for the enquiry, and the possible bias which may be encountered in each approach. As a marginal remark, I would like the authors to focus constantly on the risk associated with the „insoluble“ form of ceramic DU-oxide, essentially reaching the human organism through aerosols. This according to the title of the article.

The authors could suggest complementary epidemiological studies to be undertaken.

I would appreciate if the authors would quote the article from Padmanabham et al. (*), as this retrospective epidemiological study describes an approach which could be realized in two comparable communities of Irak: one with important risks of contamination with the DU-micro-particles, the other with an absence of such risks. The communities should be as similar as possible, regarding the professions, the economic situation, the culture and the religion.

I am not in a position to comment on the quality of the English. However, the presentation is clear to me as foreigner, except that I do not understand the word „absorbed“ in the sentence saying that insoluble forms generally take months or years to be absorbed. It probably means that the microparticles, or hot spots due to „insoluble“ DU-oxides may persist for years, or even decades.

My comments are to be given to the authors, and I would appreciate if they could accordingly amend some points of their text, especially on the distinction between the risks bound with insoluble DU-oxide particles, and other forms of uranium toxicity.

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.