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RULEMAKINGS AND
ADJUDICATIONS STAFF

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August 15, 2005

Secretary
U.S. Nuclear Regulatory Commission,
Washington, DC 20555–0001
ATTN: Rulemakings and Adjudications Staff

Dear NRC Secretary and Rule Making Staff,

Mr. Oscar Paulson of Kennecott thought that it might be of help to your committee to have a physician's input on the question of human uranium toxicity. If I were on your committee, I would like to have a feel for who was writing the letters I was reading, so I am taking the liberty to offer you a little information about myself before I make my comments. I am a practicing board certified pathologist with MD and residency training from the University of Pittsburgh. Prior to entering medical school, I did a PhD in biophysics from what was then the Department of Radiation Biology and Biophysics (now the Department of Biophysics) at the University of Rochester. As part of my coursework at the University of Rochester, I took virtually all of the available coursework on radiation biology in the department. I have written two textbooks of pathology for medical students, and have also been heavily involved with the commercial Kaplan Medical course that many medical students use to study for their board examinations. As part of that work, I have written roughly 5000 clinical scenario questions (3000 pages of text), or about half of the entire Internet question bank for that course, that over 70,000 medical students have used in the last 8 years to prepare for the required national examination taken after the second year of medical school.

I became involved with the specific problem of uranium toxicity about 2½ years ago

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when Mr. Paulson contacted me because I was apparently the only person of whom he or any of his many contacts in the uranium industry were aware that had both a PhD with training about radiation biology and an MD degree. At the time, New Mexico was considering altering ground water standards for uranium, and Mr. Paulson asked me to look critically at the uranium toxicology literature. Since then I have also been involved in discussions about ground water uranium standards in Wyoming.

Let me stress, if I may, that while I was contacted to review material by Mr. Paulson, I am not now, never have been, and never will be an employee of the uranium industry. I make enough money as a working pathologist that I will not take any money in any form for work I do on these topics. I do them as a public service because I think we need good law, that balances medical and economic needs realistically. I have stressed in all of my contacts with the broader uranium community that I will write the truth as best I understand it, and that if I think we really do have a problem with uranium, I will say so publicly. But I also recognize the danger of producing bad law that is based on a panicky reaction to something that is perceived as a problem but in reality is not.

The study that I personally find most helpful in placing the risks of uranium in an appropriate context is a NIOSH study (I.E. Pinkerton, T.F. Bloom, M.J. Hein, and E.M. Ward: *Mortality among a cohort of uranium mill workers: an update,* Occup. Environ. Med. 1004; 61:57-64) that looked at the causes of death in people who had worked in uranium mills. The study 1484 men, and compared the numbers of deaths in a variety of medical categories to what would be expected from national and Colorado mortality statistics. Many of the people whose deaths were studied had been old enough to have been working in the early period of the uranium industry, before we had learned to be very careful with uranium. They thus are thought to have had much higher chronic exposures to uranium, possibly by one or two orders of magnitude, than what we presently allow people to have.

In the context of this setting, I feel confident that (despite the withholding of judgment expected of scientists) the study authors of the NIOSH study were expecting to "prove" that the uranium mill workers had died disproportionately of causes that could be linked to uranium toxicity. Instead, what they found was that one of the very few statistically significant results in the study was that uranium mill workers had a *lower* overall mortality rate than would have been predicted by either Colorado or national mortality norms. I have discussed this surprising result with people in the uranium industry. What we think may have happened is that once it was recognized that smoking acted synergistically with many different types of stone dust (coal, asbestos, silica) to cause lung disease, the uranium industry as a whole made a very serious effort to enforce no smoking bans in work sites with uranium exposure, and also made a very serious effort to discourage workers from smoking while not at work. We postulate that these efforts to discourage smoking were successful enough to completely swamp any effect of uranium toxicity on mortality. Additionally, employee health may have been improved by the fact that the uranium mills were worried about worker health and made an effort to provide medical insurance and encourage preventive medicine. But, whatever the reason, the fact remains that in this population who might reasonably have been expected to have

significant medical problems related to uranium toxicity, the death rate was lower rather than higher than that of the general population. To me, this is a very reassuring fact.

In the detailed analysis of the causes of death in this NIOSH study, the only causes which had a statistically significant increased incidence of death over what was expected was in deaths from Hodgkin's lymphoma and deaths from non-malignant respiratory diseases, such as emphysema. The respiratory deaths were mostly seen in men hired before 1955 and the rate of death did not increase with increasing employment duration. This suggests that these respiratory deaths may have been related to factors such as smoking or inhalation of dusts, without being a specific uranium effect.

With respect to the Hodgkin's deaths, only four deaths were involved, so we are talking about a very small number of individuals. This may be an incidental clustering rather than a true uranium caused problem, because Hodgkin's disease is not one of the forms of leukemia or lymphoma that have ever been previously linked to radiation exposure. The etiology of Hodgkin's disease has been extensively studied and instead is thought to be often related to exposure to the Epstein Barr virus, whose presence can be detected in many cases of Hodgkin's disease. It would make sense that a virally-linked cancer might produce clusters of cases, and this might be what happened in this study.

Of the specifics of the many causes of death looked at in the NIOSH study of the uranium mill workers, two additional features are of note. The first feature is that no other cancer was occurring in this population at a significantly increased rate. This means that, contrary to expectation, even at the significantly increased uranium doses seen in this population, increased cancer rate was only a theoretical rather than a real risk. This suggests that our current exposure standards have a considerable margin of safety with respect to cancer risk built into them.

The second feature to specifically note in these mortality statistics is that there was no statistically significant increase in the deaths due to renal failure. This is important because we do know that extremely severe acute exposures to uranium can cause life threatening acute renal failure, that may lead to either death, or in survivors, a usually complete resolution of renal problems with time (e.g. months to years). Further, several studies (M. Limson Zamora et al: *Chronic ingestion of uranium in drinking water: A study of kidney bioeffects in humans*, Toxicological Sciences 1998, 43:68-77; M.A. Moss: *Chronic low level uranium exposure via drinking water*, Canadian thesis from Dalhousie University, Halifax, Nova Scotia, 1985; Mao, Yang et al: *Inorganic components of drinking water and microalbuminuria*, Environmental Research 1995, 71:135-140) have suggested that mild renal disease characterized by asymptomatic [with no clinical symptoms], very mild, microproteinuria [leakage of tiny amounts of protein from serum into the urine] can develop with chronic uranium exposure, and there was concern in the uranium community at large that this renal disease might tend to progress to chronic renal failure. The fact that there were no excess deaths due to renal failure in the uranium mill workers suggests that our current much lower exposure standards also have a considerable margin of safety with respect to uranium chemical toxicity for clinically significant renal disease as well.

Mr. Salsman, in both his letters to you and in his writings published in the RAD-SAF internet message chains, expresses concern about uranium related reproductive effects. He apparently is very personally concerned with these issues, and appears on the Internet to be a military member who was exposed to depleted uranium munitions and who worries whether the exposure is affecting his life and family. He raises some interesting questions, and he is correct that there is very little human literature about the topic. Most of the papers he cites are either rodent studies or review articles based at least in part on rodent studies.

Before going forward, may I offer some comments about my impression of Mr. Salsman as he appears in the discussions he has been involved with on the Internet. Mr. Salsman appears to be an intelligent man with little specific training in uranium or medical toxicity in general who has conscientiously tried to develop a knowledge base pertinent to the toxicity of uranium, particularly depleted uranium in munitions. Generally this type of background suggests that, since Mr. Salsman has clearly tried to be diligent, he might find articles that are not widely known by other people, and are thus a potentially useful contribution to discussions of uranium toxicity. However, the same background means that Mr. Salsman probably has a limited general knowledge of both medicine and medical toxicity, and the conclusions he draws from the articles he has found need to be examined with care, since he is likely to be vulnerable to mistakes in interpretation that appear to be basic to others with more experience in these fields.

Let me try to sort through what I think we do know about the reproductive issues Mr. Salsman raises, with the understanding that that he may very well have identified an area in which better human studies would be helpful.

Mr. Salsman expresses concern about the accumulation of uranium in testes. In some of his Internet comments, he mentions a testicular accumulation of 5.4 ng/g. In these references, he usually just sort of throws the number around, without indicating any of the specifics on which it was based. By so doing, he implies a general significance to the number that I was not sure was warranted, particularly since he was giving no information about the context in which it had been obtained. Because of my concern about the basis for his "fact", I found his original reference to the number, and looked it up.

The original reference is a paper called "Uranium deposition and retention in a USTUR whole body case", by J. J. Russell and R. L. Kathren, that was published in March, 2004 in Health Physics 86(3), pp 273-284. The paper is well written and represents a significant contribution to the human uranium toxicity literature. It is based on the detailed analysis of the body of a single person who died at age 83 of a stroke and donated his body for research to the U.S. Transuranium and Uranium Registries (USTUR), which had been created in 1978 to obtain tissues for analysis from volunteer donors with a known exposure to uranium. This person was apparently the first with known occupational uranium exposures to have a complete analysis of the uranium content of different body sites based on tissues taken at autopsy.

The man had had a 28 year work history as a power operator, utility operator, and metal operator in a facility that handled radioactive materials, and was known to have had significant uranium exposures. He had then been retired for approximately 20 years before his death of a cerebellar stroke. Considerable information about his work history was available, and it was thought that he had had most of his uranium exposure in aerosol form during the first 11 years of his employment, 38 to 48 years prior to his death. Based on his film badge results while employed, the paper authors estimate that he had a total lifetime whole body exposure of 11.42 rem of non-penetrating radiation and 4.33 rem of penetrating exposure. Urine had been collected periodically throughout his employment and analyzed for uranium content; based on this information the paper authors estimated that he had excreted into urine a total of 14.3 milligrams (14 thousandths of a gram) of uranium during his employment.

For those readers who are not used to thinking in grams, a gram of water has 1 milliliter volume, or about 1/5 of a teaspoon. So we are talking about this man absorbing into his body an amount of uranium over the entire course of a year what would be equivalent in volume to a few drops of water. And he is being studied because he had a potentially much higher uranium exposure than would be expected if he had not worked in the uranium industry. The paper authors point out that this suggests that he was excreting a few milligrams (thousandths of a gram) per year of uranium during this period, and that based on generally accepted uranium models for urinary excretion, that this suggests that he took into his body a few tens of milligrams of uranium every year during the first part of his employment.

At the time of the man's death, his total body load of uranium (all of the uranium in his body) was estimated to be 364.11 micrograms (364 millionths of a gram, or less than ½ of a milligram, or about 1/5 of the amount of uranium that he was excreting into urine yearly while he was employed). This estimate is a very good estimate, and was based on actual measurement of uranium concentration in about 80 soft tissue sites (which allowed the authors to calculate the uranium loads of for essentially every individual organ in the body) and about 140 bony sites.

So, what does this information mean so far? Since the man died at age 83 of stroke, his uranium exposure had pretty obviously not significantly shortened his life. Also, it means that while the man did retain uranium in his body for very long times (e.g. 4 or 5 decades), the amount retained overall was incredibly small, maybe only about 2 thousandths of the amount that had entered his body (based on assuming 20 mg per year times 10 years = 200 mg total intake into his body, and 0.4 mg [the 364 micrograms converted to milligrams] left in his body at his death, making a ratio of 0.4/200 = 0.2/100 = 2/1000). His body had actually been very efficient at clearing the uranium.

The paper goes on to present a detailed analysis of where the uranium had been found in the man's body, and compared some of this information to the relatively small amount of available information about storage of uranium in individuals who had just had normal daily life exposures to trace uranium from the environment. The appendix to the paper

has the most detailed information, and covers separately the 80 soft tissue and 140 bony sites for which they had detail. The man's exposure had predominately apparently been through inhalation of uranium containing dusts, and much of the uranium remaining in his body was concentrated in the lymph nodes (primarily those draining the respiratory tract), lung, and trachea. The concentration in the lymph nodes was the highest reached in the body, and was 1,133.83 nanograms per gram of tissue. A nanogram is a *billionth* of a gram, or a thousandth of a microgram, or a millionth of a milligram. The concentration in the trachea was 375.48 nanograms per gram of tissue, and that in the left lung was 267.98 nanograms per gram of tissue.

Mr. Salsman cites this paper because of his concern about the accumulation of uranium in the testes. The raw data reported in the appendix of the paper shows the man's right testes had a uranium concentration of 5.92 nanograms per gram of tissue (i.e. the ratio of uranium to everything else was about 6 parts in a billion) and the uranium concentration of the left testes was 3.43 nanograms per gram of tissue. These values were in the mid ranges of the concentrations reported, much less than those seen in the lymph nodes and respiratory tract, and greater than those seen in muscle, which tended to have uranium concentrations less than 1 nanogram per gram of tissue. Many other body tissues had uranium concentrations similar to that of testes, including eyes (7.50 nanograms per gram tissue), thyroid (9.81 nanograms per gram tissue), hair (6.48 nanograms per gram tissue), and diaphragm (2.48 nanograms per gram tissue). No one is suggesting that these organs tend to accumulate toxic doses of uranium.

6 parts in a billion doesn't look to me like the testes is accumulating much uranium. Mr. Salsman may have assumed that just because our modern measuring techniques have gotten so sophisticated that we can pick up extraordinarily tiny concentrations of materials, it means that they are always causing problems. That of course doesn't follow, anymore than it would mean that because a child wrote on his skin with a magic marker, it must be that the magic marker poisoned him.

Incidentally, the last paragraphs in this paper discuss the autopsy findings. Having done many autopsies myself, two things stand out in the discussion of the autopsy findings. The first is that the findings seen were typical of an older patient with severe atherosclerosis that affected many vessels in many sites of the body, and none of them would be unexpected in an older patient who had never been exposed to uranium. The second thing that stands out is that there is no mention at all of the testes (which would have certainly been sampled as part of the autopsy protocol), which means to me that the testicular findings were so typical of what is usually seen in an autopsy of an older individual, that the authors didn't even choose to comment on them - which certainly wouldn't have been the case if the paper authors had thought that the testes were a significant source of uranium pathology.

Mr. Salsman in his Internet writings makes reference to a second important paper that is worth discussing here in the context of his letter to your committee. This paper is "A review of the effects of uranium and depleted uranium exposure on reproduction and fetal development", by Darryl P Arfsten, Kenneth R Still, and Glenn D Ritchie (Toxicology

and Industrial Health 2001; 17:180-191). These authors are at Wright-Patterson Air Force Base, and have been concerned about the potential effects on Persian Gulf and Kosovo veterans of having been exposed to depleted uranium. Their paper is a well-referenced review paper (with no new data) that explores what we know about uranium and depleted uranium and their effects of reproduction and fetal development.

One point that the authors of this paper make with which I strongly agree is that there may be a significant possibility of true uranium poisoning if shrapnel composed of depleted uranium is left permanently in someone's body because it has lodged in a surgically inaccessible site. Because of the possibility of long-term effects, I think we would probably be wise to try to remove if at all surgically feasible, any shrapnel fragments that do contain uranium. However, that topic lies beyond the scope of what your committee is trying to do, and has no bearing on whether our present occupational exposure limits for uranium are set correctly. A person who gets in a war-time setting a piece of depleted uranium containing shrapnel lodged permanently in his body has probably massively exceeded current occupational limits anyway. Whether the very real protection offered against munitions by depleted uranium (which is one of the physically strongest material we have) shielding (with potential of significantly saving lives in a wartime setting) outweighs the risks of poisoning if shrapnel cannot be removed is a question for the military, and does not seem to be to apply to the decisions your committee is making. Additionally, even if we were to choose to not use the depleted uranium, exposures could still occur if the enemy force used it against our troops in shield penetrating munitions.

The Arfsten paper reviews the scanty human literature pertaining to uranium effects on human reproduction and fetal development. One paper they cite had found an altered frequency of female offspring among male uranium workers, which was interpreted as suggesting a possible effect on sperm. To me this sounds like suggestive data, but too weak to base a specific decision on at this point. Another study the Arfsten paper mentions looked at male uranium miners from Namibia, Africa (who probably had very different occupational exposures and general medical backgrounds that American uranium miners) and found increased levels of sister chromosome exchanges in white blood cells (a marker for potential genetic abnormalities in sperm) and decreased testosterone levels as compared to control subjects who did not work in the uranium industry. A third paper cited by the Arfsten paper reported a statistical association between maternal exposure to mine tailings and unfavorable birth outcomes in Navajo Indians living near Shiprock, New Mexico. While the exposure was cited as maternal exposure to mine tailings, I wondered when thinking about this topic whether a more likely source of exposure might be from private well water containing high concentrations of naturally occurring uranium in this uranium rich area, which might have ground water with uranium concentrations up to two orders of magnitude greater than what is allowed in public water supplies. (The permissible concentration of uranium in private wells is at the moment unregulated due to a loophole in the current federal drinking water standards.) In any event, if the report is reliable, it does suggest the possibility of adverse effects, but does not address the topic of whether the exposures producing the effects were already above existing standards or not.

The Arfsten paper also reviews several studies that followed Persian Gulf War veterans that had been in tanks and fighting vehicles hit with (presumably enemy) munitions containing depleted uranium penetrators. Some of these veterans had been hit with uranium containing shrapnel that could not be surgically removed, and in follow-up, a few of these veterans were excreting heavy concentrations of uranium in urine (up to 39.1 micrograms of uranium per gram of creatinine, which is up to 1000 to 10,000 times that excreted by unexposed individuals). Some of the individuals had also been exposed to aerosolized uranium in the attacks. This population appears to have developed some statistically significant level of subtle neurocognitive (brain reasoning) impairment. The results on sperm numbers and motility were much more equivocal - the 1997 study showed no difference in sperm characteristics, while the 1999 study showed significantly elevated sperm counts and sperm motility (e.g. improved rather than impaired sperm physiology). Again, to put the studies in context, carrying uranium containing shrapnel around in your body almost certainly exceeds current occupational limits for uranium exposure.

The Arfsten paper also looked at papers reporting on the effects on rat reproductive and developmental problems related to exposures to uranium. One study that looked at depleted uranium pellets implanted into female rats was unable to demonstrate any impact on maternal or fetal parameters related to the rats' pregnancies. Other studies of rats fed very high concentrations of uranium nitrate (e.g. 2% of the food was uranium; a corresponding dose in humans might be a tablespoon of uranium salts daily - compare that to the doses that the man whose body after death was evaluated for uranium concentrations got!) showed a decrease in litter frequency with the high uranium doses. Other high dose rodent studies showed testicular atrophy in rats.

Despite these fairly convincing rodent studies, the significance in the context of your committee is unclear. Partly, these studies were all at such high dose studies that it is unclear that the present uranium exposure limits aren't already set low enough that people in whom the occupational exposures are within current limits aren't already protected. Additionally, the studies don't have enough dosing information in them to be able to accurately estimate what human levels of toxicity would trigger the reproductive effects. This means that, even if your committee were to decide that you wanted to worry about the reproductive toxicity effects, it is not at all clear that you would be able to figure out what an appropriate acceptable exposure would be. We just aren't at the point that new standards can be set, if desired, in a reasonable way.

This is a developing field, and, because of the interest in the Gulf War veterans exposures, we can anticipate that the problem of whether or not there is any significant reproductive toxicity at current levels of acceptable uranium exposures (which I anticipate will prove adequately protective) will become better defined over the next ten years. In the mean time, we already have strict occupational exposure limits about uranium, and I personally do not think that you need to tinker with them at this time.

I appreciate your having read this long letter and I hope that my comments may be of

some value to your committee. With thanks for your attention,

Nancy Standler, MD PhD

Nancy Standler, MD PhD, pathologist
Valley View Hospital, Cedar City, Utah

**From:** "Nancy Standler" <nancy.standler@ihc.com>
**To:** <secy@nrc.gov>
**Date:** Wed, Aug 17, 2005 2:13 AM
**Subject:** Docket No PRM-20-26 - James Salsman petition

Dear NRC -
Attached are my comments on James Salsman's petition.
Nancy Standler, MD PhD

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| **Creation Date:** | Wed, Aug 17, 2005 2:12 AM |
| **From:** | "Nancy Standler" <nancy.standler@ihc.com> |
| **Created By:** | nancy.standler@ihc.com |

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| Mime.822 | 130815 | |

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