

**URANIUM TOXICITY LITERATURE**  
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**Forward**

The health effects of depleted uranium as a consequence of the use of this heavy metal in military munitions has become a highly charged, political controversy. This document contains approximately 300 entries and was compiled to provide a comprehensive list of references from the scientific and medical literature regarding uranium toxicity. There is an accompanying document that provides a list of references that describe the chemical properties of uranium, how it is measured in urine, sea water and other environmental matrices, and some approaches to remediation of environmental contamination by uranium and related heavy metals. There have been several recent reports by prestigious organizations that summarize the health effects of depleted uranium; these are listed below. The reader should be aware that these reports were intended to evaluate whether depleted uranium munitions could be the cause of at least some of the symptoms of Gulf War Syndrome observed in soldiers serving in the Persian Gulf conflict in 1991. These reports have generally limited their scope to health effects of uranium in humans, for which there is meager data. Epidemiology of uranium workers indicates minor health risks in this population, but it is necessary to keep in mind that these workers have been closely monitored and protected from exposure since the inception of this industry. The monitoring and protection of military personnel has not been so rigorous. These reports are: The health hazards of depleted uranium munitions. Part I. Radiological Effects. and Part II. Non-

Radiological Effects and Environmental Impact. Published by The Royal Society, March 2002. This report can be found at: [www.royalsoc.ac.uk](http://www.royalsoc.ac.uk)

Gulf War and Health. Vol 1. Depleted uranium, sarin, pyridostigmine bromide, vaccines. Committee on Health Effects Associated with Exposures During the Gulf War. Institute of Medicine, 2000. This report can be found at: [www.nap.edu](http://www.nap.edu)

Depleted Uranium. Published by the World Health Organization. This report can be found at: [www.who.int/environmental\\_information/depleted\\_uranium.htm](http://www.who.int/environmental_information/depleted_uranium.htm)

## 1] Biochemical Studies - Binding to DNA and DNA Cleavage

Uranium (uranyl salts) has been used for more than 40 years to stain DNA for electron microscopy. Other stains were favored by electron microscopists, which may be due to the more recent findings (1990s) that uranyl ion can catalyze hydrolysis of DNA (strand breaks) in the presence of light. The binding of DNA to nucleic acids and nucleotides and its catalysis of chemical modification of these molecules would clearly implicate this heavy metal as a cytotoxin.

Electron Stains: I. Chemical Studies on the Interaction of DNA with Uranyl Salts. C. Richard Zobel and Michael Beer, *J. Biophys. Biochem. Cytol.* **10**, 336-346, 1961. Discusses the effects of pH, salt concentration and structural integrity of DNA on the chemical interaction of uranyl salts, using spectrophotometric characterization of binding.

Preferential staining of nucleic acid-containing structures for electron microscopy. H.E. Huxley and G. Zubay, *J. Biophys. Biochem. Cytol.* **11**, 273-296, 1961. Used uranyl acetate staining to reveal excellent fine structure in nucleohistone fibers. Purified DNA can take up nearly its own dry weight of uranyl acetate from 2 % fixing solution, indicating high affinity.

Metachromasia through uranyl ions: a procedure for identifying the nucleic acids and the nucleotides. D. Gr. Constantinescu and Elena Hatieganu, *Anal. Biochem.* **62**, 584-587, 1974. Describe binding of uranyl ions through phosphate groups of nucleic acids and nucleotides.

Uranyl salts as photochemical agents for cleavage of DNA and probing of protein-DNA contacts. Peter E. Nielsen, Claus Jeppesen and Ole Buchardt, *FEBS Letts.* **235**, 122-124, 1988. Used uranyl acetate and nitrate to bind uranyl ion to single stranded DNA and induce nicks (cleavage) with visible light at 420 nm. Nicks are random, but proteins bound to DNA protect that region.

Uranyl photoprobing of a four-way DNA junction: evidence for specific metal ion binding. Niels Erik Møllegaard, Alastair I.H. Murchie, David M.J. Lilley and Peter E. Nielsen, *EMBO J.* **13**, 1508-1513, 1994. Indicates uranyl, hexaminecobalt(III) and spermidine compete for the same high affinity binding site at a four-way DNA junction.

DNA binding and photocleavage by uranyl salts. Peter E. Nielsen, Catharina hiort, Søren Holst Sønnichsen, Ole Buchardt, Otto Dahl and Bengt Nordèn, *J. Amer. Chem. Soc.* **114**, 4967-4975, 1992. Describe binding of uranyl ion in the minor groove of DNA to induce photocleavage. The binding constant is estimated to be  $10^{10} \text{ M}^{-1}$  at pH 4. Photocleavage not influenced by  $\text{O}_2$  and occurs either 3' or 5' to the deoxyribose.

Enhanced uranyl photocleavage across the minor groove of all (A/T)<sub>4</sub> sequences indicates a similar narrow minor groove conformation. Søren Holt Sønnichsen and Peter E. Nielsen, *J. Molec. Recogn.* **9**, 219-227, 1996. Shows preferential cleavage of dsDNA in the minor groove at AT rich regions, i.e., least polar region of DNA molecules.

## 2] Cytogenetic Toxicity and DNA Mutations

The following papers show that uranium (in various forms) can cause chromosomal damage and genetic aberrations, such as increases in sister chromatid exchanges and micronuclei formation, which are indicative of DNA strand breaks. These changes are often implicated in carcinogenesis. Increased strand breaks in germ cells (sperm and ova) can lead to greater risk of birth defects in offspring.

Cytogenetic toxicity of uranyl nitrate in Chinese hamster ovary cells. R.H. Lin, L.J. Wu, C.H. Lee and S.Y. Lin-Shiau, *Mutation Research* **319**, 197-203, 1993. Uranyl nitrate decreased the viability of CHO cells in a dose-related fashion, with IC<sub>50</sub> (conc for 50% inhibition) was 0.049 mM. At 0.01 to 0.3 mM uranyl nitrate decreased cell cycle kinetics, increased frequency of micronuclei and sister chromatid exchange and augmented chromosomal aberrations. Results indicates that uranyl nitrate causes genotoxicity and cytotoxicity in CHO cells and provides the biochemical basis for teratogenic effect of U on developing fetal mice (Domingo et al, *Toxicology*, 55, 143-152, 1989).

Cytotoxic effect of uranium dioxide on rat alveolar macrophages. DR Tasat, BM deRey, *Environmental Research*, **44**, 71-81, 1987. This is an important study in that it shows that alveolar macrophages (immune cells responsible for clearing debris and inhaled particulates from the lungs) grown in culture are destroyed by UO<sub>2</sub> particles of average 0.6 micron diameter. The proportion of cells that devoured uranium particles reached a maximum at 6 hr, and the average time for uranium containing cells to become nonviable was about 16 hr. Beyond 16 hr, dead cells predominated. Cell damage correlated with uranium content. Immediately after phagocytosis the U particles were found in phagocytic vacuoles, but were later found outside these vacuoles as a result of membrane damage. Although the authors don't mention the likelihood of UO<sub>2</sub> being oxidized and solubilized by active radical producing enzymes in these organelles, it is likely that this is happening.

Uranyl acetate causes DNA single strand breaks in vitro in the presence of ascorbate (vitamin C). M. Yazzie, S.L. Gamble, E.R. Civitello and D.M. Stearns, *Chem. Res. Toxicol.* **16**, 524-530, 2003. This study showed that uranyl ion forms a 1:1 complex with ascorbate that catalyzes plasmid relaxation (caused by DNA strand breaks) in a concentration dependent manner. Increasing the ratio of ascorbate to U had no effect and dehydroascorbate was not detected as a product. Hydroxyl radical scavengers did not inhibit the plasmid relaxation, indicating a Fenton-type reaction was not responsible for this effect [in contrast to Miller et al., *J. Inorg. Biochem.*, 91, 246-252, 2002]. Catalase inhibited strand breaks by ca. 40%, suggesting H<sub>2</sub>O<sub>2</sub> involvement, but not hydroxyl radical or similar reactive species, nor is dehydroascorbate formed. The authors suggest DNA strand breaks may be via more than one mechanism, depending on conditions.

Transformation of human osteoblast cells to the tumorigenic phenotype by depleted uranium-uranyl chloride. A.C. Miller, W.F. Blakely, D. Livengood, T. Whittaker, J. Xu, J.W. Ejniak, M.M. Hamilton, E. Parlette, T. St. John, H.M. Gerstenberg and H. Hsu, *Environmental Health Perspectives* **106**, 465-471, 1998. Show that 10 :M uranyl chloride transforms immortalized HOS to tumorigenic phenotype. The DU transformants are characterized by anchorage-indep growth, tumor formation in nude mice, expression of high levels of the *k-ras* oncogene, reduced production of Rb tumor suppressor protein and elevated levels of sister chromatid exchanges. There was a 9.6 fold increase in transformations in

U treated cells rel to controls. By comparison, Ni gave 7.1 fold increase in transformations.

Observation of radiation-specific damage in human cells exposed to depleted uranium: dicentric frequency and neoplastic transformation as endpoints. AC Miller, J Xu, M Stewart, K Brooks, S Hodge, L Shi, N Page, D McClain, *Radiation Protection Dosimetry* **99**(1/4), 275-278, 2002. Using human osteoblast cells in culture, uranyl nitrate made with depleted uranium was compared with other isotope compositions with varying specific activity, and compared to nickel and tungsten for toxic effects. They showed that depleted uranium exposure resulted in increased dicentric (chromosomes with two centromeres) frequencies compared to nickel or tungsten, but higher specific activity of radiation with constant chemical concentration for uranium resulted in a radiation-dependent increase in dicentrics. It is concluded that this effect on chromosomal aberration is due to alpha radioactivity.

Depleted uranium-catalyzed oxidative DNA damage: absence of significant alpha particle decay. A.C. Miller, M. Stewart, K. Brooks, L. Shi, N. Page, *Journal of Inorganic Biochemistry* **91**, 246-252, 2002. Shows thymine glycol and 8-hydroxydeoxyguanosine are formed as a result of oxidative attack on DNA, indicating the uranyl ion is involved in a Fenton type reaction, similar to iron. Showed that hydrogen peroxide and ascorbate augment the damage. These results indicate U acts through generation of oxy radicals, with radiologic damage being minimal.

Plutonium-catalyzed oxidative DNA damage in the absence of significant alpha-particle decay. HG Claycamp, D Luo, *Radiation Research*, **137**, 114-117, 1994. This study used a low activity isotope, Pu-242, to show there was oxidation of DNA bases characteristic of hydroxyl radical damage, using ascorbate and hydrogen peroxide to generate hydroxyl radical in a Fenton type reaction, similar to that catalyzed by iron. The Pu(III) nitrate was nearly 5 times more efficient than iron at pH 7. This indicates plutonium may be carcinogenic from both its radiolytic activity as well as its chemical reactivity. Miller et al. have shown similar reactions catalyzed by uranium (above).

Hydrogen peroxide-induced base damage in deoxyribonucleic acid. WF Blakely, AF Fuciarelli, BJ Wegher, M Dizdaroglu, *Radiation Research*, **121**, 338-343, 1990. This study did not use uranium, but shows that hydrogen peroxide will oxidize DNA bases, most likely through metal catalyzed Fenton type reactions. DMSO, a free radical scavenger inhibited this oxidation by about 40 to 60%, but higher concentrations of this scavenger would inhibit no further than 60%. Metal chelating agents were highly effective at suppressing these DNA base oxidations. This study is significant in the context of uranium catalyzed oxidation of DNA bases in the presence of hydrogen peroxide.

Uranium reactions with hydrogen peroxide studied by EPR-spin trapping with DMPO. MM Hamilton, JW Ejniak and AJ Carmichael, *Journal of the Chemical Society, Perkin Transactions 2*, 2491-2494, 1997. This study shows that uranyl nitrate in solution with hydrogen peroxide in the presence of the spin trapping agent, DMPO, generates the typical hydroxyl radical adduct of DMPO as measured by EPR spectrometry. This provides evidence that uranyl ion catalyzes hydroxyl radical mediated oxidations, much like iron or copper ions in solution.

Depleted uranium-uranyl chloride induces apoptosis in mouse J77s macrophages. J.F. Kalinich, N. Ramakrishnan, V. Villa, D.E. McClain, *Toxicology*, **179**, 105-114, 2002. Found treatment of cells with 1, 10 or 100 :M U decreased viability of cells within 24 hr. Changes in membrane structure was indicative of the apoptotic process. Changes were evident in 2 hr with the 100 :M conc. This means that cells responsible for clearing DU are being killed by this metal ion.

Genomic instability in human osteoblast cells after exposure to depleted uranium: delayed lethality and

micronuclei formation. A.C. Miller, K. Brooks, M. Stewart, B. Anderson, L. Shi, D. McClain, N. Page, *Journal of Environmental Radioactivity* **64**, 247-259, 2003. Showed that U stimulates delayed production of micronuclei, up to 36 days after exposure, whereas gamma radiation returned to normal after 12 days. Micronuclei formation from U exposure was greater than for gamma-irradiated cells (equal radiation dose) or nickel treated cells. Micronuclei arise from DNA double strand breaks that are not rejoined and are implicated in human carcinogenesis.

Analysis of chromosomal aberration frequencies in the peripheral blood lymphocytes of smokers exposed to uranyl compounds. P.A. Prabhavathi, S.K. Fatima, M.S. Rao, and P.P. Reddy, *Mutation Research* **466**, 37-41, 2000. Studied 115 workers at a nuclear fuel manufacturing facility (in India) for chromosomal aberrations and compared them with 94 smokers and 118 nonsmokers who were not exposed to uranium. U exposed smokers had signif. more chrom. aberrations than smokers not exposed and unexposed nonsmokers had the least aberrations.

Neoplastic transformation of human osteoblast cells to the tumorigenic phenotype by heavy metal-tungsten alloy particles: induction of genotoxic effects. A.C. Miller, S. Mog, L. McKinney, L. Luo, J. Allen, J. Xu and N. Page, *Carcinogenesis* **22**, 115-125, 2001. Compares the relative neoplastic transformation potential of tungsten-nickel alloys and their potential for causing DNA strand breaks leading to micronuclei formation. This shows that the tungsten-nickel alloys have slightly greater potency than Ni alone, similar to uranyl ion shown in previous study [Miller et al., *Envir. Health Persp.* 106, 465-471, 1998, see above].

Suppression of depleted uranium-induced neoplastic transformation of human cells by the phenyl fatty acid, phenyl acetate: chemoprevention by targeting the p21RAS protein pathway. A.C. Miller, J. Xu, M. Stewart and D. McClain, *Radiation Research* **155**, 163-170, 2001. This study was done as a follow up to a previous study [Miller et al., *Envir. Health Persp.* 106, 465-471, 1998, above] that shows transformation of human cells to tumorigenic phenotype following exposure to U. This paper shows that phenyl acetate (a potential chemotherapeutic agent) could prevent transformation to the tumorigenic phenotype and decreased membrane associated p21RAS protein, an inducer of cell transformation. Phenyl acetate can interfere with p21 processing by blocking the mevalonate pathway and farnesol synthesis. Farnesylation of p21 results in its membrane association. The authors also speculate that uranyl ions may catalyze free radical that could be involved in transformation. They do not mention possible effects that phenyl acetate might have on the bystander effect (see following section).

Solubility and hemolytic activity of uranium trioxide. WI Stuart, RB Adams, HE Smith, *Environmental Research* **18**, 385-396, 1979. This was a rather complex study of the dissolution of  $UO_3$  in aqueous solutions of different salts and the *in vitro* hemolytic properties of different uranyl salts resulting from the dissolution.

Induction of chromosomal aberrations in male mouse germ cells by uranyl fluoride containing enriched uranium. Q Hu and S Zhu, *Mutation Research* **244**, 209-214, 1990. Frequencies of chromosomal aberrations in spermatogonia and primary spermatocytes were dependent on doses of uranyl fluoride injected into the testes.

### **3] The Bystander Effect and Low Dose Effects in Radiation Induced Cytotoxicity**

The following articles show that radiation damage can induce signals in cells that are sent to neighboring cells that have not received direct radiation. This “bystander effect” can result in far more

cellular damage than expected for the number of cells that are directly hit by  $\nabla$ -particles. This information has been neglected in most arguments suggesting that internalized depleted uranium would not have sufficient radiation effects to produce a significant increase in cancers. These papers discuss the implications of this effect for radon gas exposure, but it would also apply to  $\nabla$ -particles emitted by any radioactive element, including uranium or plutonium. It was argued “If DNA damage were to occur in bystander cells in vivo, and these cells survived such damage, these results would impact significantly on the assessment of cancer risk initiated by low fluence exposures to  $\nabla$ -radiation.” [Azzam et al., PNAS, 98, 478, 2001, see below] Furthermore, cells that may die from such exposures can potentially promote tumor growth.

Induction of sister chromatid exchanges by extremely low doses of  $\nabla$ -particles. H. Nagasawa and J.B. Little, *Cancer Research* **52**, 6394-6396, 1992. Chinese hamster ovary cells grown in culture were irradiated with low doses of  $\nabla$ -particles (31 mrad) during G<sub>1</sub> ((pre-DNA synthesis) phase. Found that 30% of cells had increased frequency of sister chromatid exchange (SCE), even though less than 1% of cells would have been traversed by an  $\nabla$ -particle. Although the significance of SCE isn't clear, it is generally recognized that SCE can lead to increased genetic mutations in daughter cells. Authors suggest that intercellular communication may be responsible for this phenomenon.

Mutagenic effects of a single and exact number of  $\nabla$ -particles in mammalian cells. T.K. Hei, L-J. Wu, S-X. Liu, D. Vannais, C.A. Waldren and G. Randers-Pehrson, *Proceedings of the National Academy of Sciences* **94**, 3765-3770, 1997. Using hamster-human hybrid cells in culture, showed that single  $\nabla$ -particle traversal was only slightly cytotoxic (>80% survival) but highly mutagenic (110 mutants/100,000 survivors). Cytotoxicity and mutant induction were both dose dependent.

Unexpected sensitivity to the induction of mutations by very low doses of alpha-particle radiation: evidence for a bystander effect. H. Nagasawa and J.B. Little, *Radiation Research* **152**, 552-557, 1999. Found a linear dose response for radiation induced mutations in Chinese hamster ovary cells in culture in the dose range of 5 cGy to 1.2 Gy (>20 fold range), but the response was not linear below 5 cGy, instead it was much higher than expected from extrapolation of the linear data. There was a nearly 5 fold increase in mutations over expected response at lowest doses studied. This supports the bystander effect, i.e., mutations arising in nonirradiated cells through signals from neighboring cells exposed to radiation.

Induction of a bystander mutagenic effect of alpha particles in mammalian cells. H. Zhou, G. Randers-Pehrson, C.A. Waldren, D. Vannais, E.J. Hall and T.K. Hei, *Proc. Natl. Acad. Scis.* **97**, 2099-2104, 2000. Showed that genetic mutations were about 3 fold higher than expected if one assumes no bystander effect. Also showed that the types of mutations induced were different from those occurring spontaneously (without radiation). Radical scavengers had no effect on mutagenicity. These results further support intercellular communication inducing the bystander effect.

Radiation Risk to low fluences of  $\nabla$ -particles may be greater than we thought. H. Zhou, M. Suzuki, G. Randers-Pehrson, D. Vannais, G. Chen, J.E. Trosko, C.A. Waldren and T.K. Hei, *Proc. Natl. Acad. Scis.* **98**, 14410-14415, 2001. It was shown in this paper that when 10% of cells in a confluent population were hit with a single  $\nabla$ -particle the result was similar to that observed when all cells are irradiated. It was found that the bystander effect could be eliminated by treating the cell culture with octanol, a chemical that blocks intercellular communication through gap junctions (direct communication channels between contiguous cells).

The bystander effect in radiation oncogenesis: I. Transformation in C3H 10T $\frac{1}{2}$  cells in vitro can be initiated in the unirradiated neighbors of irradiated cells. S.G. Sawant, G. Randers-Pehrson, C.R. Geard, D.J. Brenner and E.J. Hall, *Radiation Research* **155**, 397-401, 2001. Similar results to work by Zhou et al. (above), but using a different cell line.

Direct evidence for the participation of gap junction-mediated intercellular communication in transmission of damage signals from  $\nabla$ -particle irradiated to nonirradiated cells. E.I. Azzam, S.M. de Toledo and J.B. Little, *Proc. Natl. Acad. Scis.* **98**, 473-478, 2001. Using genetically engineered cells with compromised gap junctions, showed that the bystander effect is mediated by gap junctions, i.e., nonirradiated cells respond to radiation induced damage in neighboring cells. They found increased expression/activation of specific biochemical markers that are induced by stress which also correlated with induction of DNA damage, seen in the increased number of micronuclei in cells arising from DNA double-strand breaks.

Direct evidence for a bystander effect of ionizing radiation in primary human fibroblasts. OV Belyakov, AM Malcolmson, M Folkard, KM Prise and BD Michael, *British Journal of Cancer* **84(5)**, 674-679, 2001. Individual primary human fibroblasts within a population of 600 to 800 cells were targeted with 1 to 15 He ions (effectively alpha particles) delivered through the center of the nucleus with an accuracy of  $\nabla 2$  micron. Even though only a single cell had been targeted, when scored 3 days later, there were typically an additional 80 to 100 damaged cells in surviving populations of about 5000 cells. The yield of damaged cells was independent of the number of charged particles delivered to the targeted cell.

Review: Radiation-induced bystander effects: past history and future directions. C. Mothersill and C. Seymour, *Radiation Research* **155**, 759-767, 2001. (Not reviewed yet)

#### **4] Uranium Binding to Membranes, Proteins and Enzyme Inhibition**

The reaction of Pu(IV) with the iron transport system in human blood serum. Stover, B.J., Bruenger, F.W. and Stevens, W. *Radiation Research* **33**, 381-394, 1968. Pu(IV) ion in human blood serum binds to low molecular weight proteins and forms complexes with small ions. The majority of protein bound Pu(IV) was bound to the iron transporting protein, transferrin if iron was half the maximum capacity, but iron would displace Pu(IV) when added in excess. Uranyl ion also binds to transferrin [see Cooper et al, Uranium Aerosols section].

The effect of uranyl nitrate in intestinal transfer of hexoses. H Newey, PA Sanford, DH Smyth, *Journal of Physiology* **186**, 493-502, 1966. At low concentration (0.3 mM), uranyl nitrate inhibited glucose but not galactose transport in intestinal cells, but at higher concentration (3 mM) uranyl nitrate inhibited transport of both sugars. It is suggested that there are two different glucose transport mechanisms, one sensitive to uranyl ion and one insensitive.

Regulatory mechanisms of cellular respiration. I. The role of cell membranes: uranium inhibition of cellular respiration. Barron, E.S.G., Muntz, J.A. and Gasvoda, B. *Journal of General Physiology* **32**, 163-178, 1948. Uranyl nitrate was found to bind several proteins, including plasma albumin, and inhibits enzymes involved in cellular respiration in yeast. Glucose oxidation was completely inhibited by 0.1 mM uranyl nitrate in yeast. Addition of a large excess of phosphate or small excess citrate would reverse the inhibition. Several other factors were reported in this study.

Uraniosomes produced in the synovial membrane by uranyl acetate. Ghadially, F.N., Lalonde, J.-M.A.

and Yong, N.-K. *Pathology* **14**, 121-127, 1982. Injection of uranyl acetate in the knee joint of rabbits produced lysosomal bodies with electron dense crystals labeled “uraniosomes” in type A and type B synovial cells, subsynovial macrophages and lipocytes. U deposits were also seen in extracellular fluid. The deposits contained U, potassium and phosphorus, with traces of Ca and S in some uraniosomes.

Uraniosomes produced in cultured rabbit kidney cells by uranyl acetate. Ghadially, F.N., Lalonde, J.-M.A. and Yang-Steppuhn, S. *Virchows Archive [Cell Pathology]* **39**, 21-30, 1982. Treatment of rabbit kidney cells with uranyl acetate caused formation of U loaded lysosomal bodies labeled uraniosomes. All uraniosomes and extracellular U deposits contained K, Ca and P, with traces of S in some deposits.

An ultrastructural evaluation of the cell organelle specificity of the uranaffin reaction in tow human endocrine neoplasms. Payne, C.M., Nagle, R.B., Borduin, V.F. and Kim, A. *Journal of Submicroscopic Cytology* **15(3)**, 833-841, 1983. The uranaffin reaction is a measure of uranium (uranyl acetate) binding and uptake by organelles. This study showed electron dense U in nucleus, the nuclear chromatin, nucleolus, and inter- or perichromatinic granules when saline was used as the staining medium. If cacodylate buffer was used in place of saline, the reactivity was much different and gave more crystalline appearance to the U deposits, with densities in the cytosol, endoplasmic reticulum., mitochondria and lysosomes, as well as the nucleus.

An ultrastructural cytochemical stain specific for neuroendocrine neoplasms. Payne, C.M., Nagle, R.B. and Borduin, V.F. *Laboratory Investigations* **51**, 350-365, 1984. This was a continuation of the above study, looking at non-neoplastic tissues as well as other neoplastic tissues. Neuroendocrine neoplasms showed abundant staining in secretory granules. Non-neuroendocrine neoplasms were negative for staining in secretory granules. This staining technique may be useful as a specific marker for distinguishing types of neoplasms.

An experimental test of new theoretical models for the electrokinetic properties of biological membranes: the effect of  $\text{UO}_2^{++}$  and tetracaine on the electrophoretic mobility of bilayer membranes and human erythrocytes. Pasquale, L., Winiski, A., Oliva, C., Vaio, G. and McLaughlin, S. *Journal of General Physiology* **88**, 699-717, 1986. Showed that uranyl ion binds to phosphate groups of phospholipids in a bilayer membrane, but does not well to sialic acid groups on membranes. Uranyl binds strongly to egg phosphatidyl choline vesicles, changing their zeta potential from 0 to +40 mV and affects mobility of phosphatidyl serine vesicles, but shows much less effect on vesicles formed from mixtures of phosphatidyl choline and negatively charged gangliosides or erythrocytes. It is suggested that gangliosides protruding from the surface of vesicles exert hydrodynamic drag and the uranyl charges on the surface exert a smaller effect on mobility than charges located away from the surface, such as sialic acid groups.

Use of uranyl ion in membrane transport studies. Cirillo, V.P. and Wilkins, P.O. *Journal of Bacteriology* **87**, 232-233, 1964. This short note describes using uranyl nitrate to inhibit loss of sugars from microbial cells in membrane transport studies.

Paired helical filaments in corticobasal degeneration (CBD): the fine fibrillary structure with NanoVan. Elzbieta Tracz, Dennis W. Dickson, James F. Hainfeld, Hanna Ksiezak-Reding, *Brain Res.* **773**, 33-44, 1997. Discuss using uranyl acetate, aurothioglucose, and NanoVan (vanadium compd) to identify CBD filaments by electron microscopy. This shows that uranyl ion binds to paired helical filaments in nerve tissue. It isn't certain what effect uranyl ion may have on neurodegenerative diseases.

Remarkable affinity and selectivity for  $\text{Cs}^+$  and uranyl ( $\text{UO}_2^{2+}$ ) binding to the manganese site of the apo-water oxidation complex of photosystem II. G.M. Ananyev, A. Murphy, Y. Abe and G.C. Dismukes, *Biochemistry* **38**, 7200-7209, 1999. Studied binding of several different alkali and alkaline earth (divalent) metal ions to apo-water oxidizing complex of PSII in spinach (that had Mn(II), Ca(II) and Cl- removed). Uranyl ion strongly inhibits photooxidation of  $\text{Mn}^{2+}$  in PSII. Uranyl  $K_d = 15.3 \text{ :M}$ . They argue that uranyl may block first or second photo-activation step, or alternatively accelerate the decay of  $\text{IM}_1$  (first oxidized intermediate). One must keep in mind that uranyl is a strong oxidant, just like the photooxidized Mn complex in PSII.

## 5] Nephrotoxicity

The nephrotoxicity of uranium was recognized in the 19<sup>th</sup> century. Hodge gives a good review of the history of uranium poisoning prior to the Manhattan Project. Other reviews of uranium toxicity in the decades following World War II, when the nuclear industry grew in those countries with nuclear capabilities, focus mostly on the kidney damage caused by uranium.

Pharmacology and Toxicology of Uranium Compounds, C. Voegtlin and H.C. Hodge, eds., McGraw-Hill Book Co., Inc., New York, 1949. This is a two-volume set, with >1000 pages, 16 chapters on various aspects of uranium toxicity and one chapter on fluorine toxicity. This early treatise provides reports of the extensive studies that had been carried out on uranium toxicity prior to 1949, including absorption of uranium compounds through the skin, in the conjunctiva of the eyes, inhalation, direct injection into the blood stream, administration in food or water, distribution of U in the body, actions on enzymes and proteins, tolerance and mechanisms of action. It is clear from reading this that it was well known in 1949 that uranium is toxic to humans, as well as animals, and can be absorbed into the body by several routes of exposure, whether in the form of soluble uranium compounds in solution or as suspensions of uranium oxides.

A history of uranium poisoning (1824-1942). H.C. Hodge, in Handbook of Experimental Pharmacology, New Series XXXVI, Uranium, Plutonium, Transplutonic Elements, H.C. Hodge, J.N. Stannard and J.B. Hursh, eds., Springer-Verlag, New York, 1973, pp. 5-69.

Animal Experiments. C.L. Yuile, in Handbook of Experimental Pharmacology, New Series XXXVI, Uranium, Plutonium, Transplutonic Elements, H.C. Hodge, J.N. Stannard and J.B. Hursh, eds., Springer-Verlag, New York, 1973, pp. 165-196. A review of the many aspects of uranium toxicity from animal studies.

Oral ingestion of uranium by man. JB Hursh, WR Neuman, T Toribara, H Wilson and C Waterhouse, *Health Physics* **17**, 619-621, 1969. (Not reviewed yet).

The behavioral and chemical toxicity of U in the kidney: a reassessment. RW Leggett, *Health Physics* **57(3)**, 365-383, 1989. This gives a thorough comprehensive review of uranium nephrotoxicity, with detailed descriptions of what is known about how the kidney handles uranium and the specific sites of damage to kidney cells by uranium. Although published in 1989, there is relatively little to add in terms of our current understanding of uranium toxicity to the kidney. This paper is strongly recommended for anyone wishing to understand the biomedical aspects of uranium nephrotoxicity.

A histological kidney study of uranium and non-uranium workers. J.J. Russell, R.L. Kathren, S.E. Dietert, *Health Physics* **70(4)**, 466-472, 1996. Kidney tissue sections were inspected by pathologists

for damage from uranium exposure in 7 uranium industry workers on autopsy and compared with six workers who would have had no known uranium exposure. The results showed similar kidney damage in control (unexposed) individuals compared to exposed individual, with 3 of 7 kidneys in the exposed group getting overall abnormal rating and 4 of 6 in the control group getting an abnormal rating, although 4 of the 7 exposed had overall scores above the mean, while only 2 of the 6 controls had scores above the mean. It is interesting to note that on exposed individual with by far the highest U exposure history (hundreds of mg vs tens of milligrams for next highest) had scores of zero for all microscopic diagnoses (the only kidneys to have overall scores of less than 3 in both groups).

Toxicity in man of hexavalent uranium following intravenous administration. A.J. Luessenhop, J.C. Gallimore, W.H. Sweet, E.G. Struxness, J. Robinson, *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine* **79**, 83-100, 1958. Terminal patients with brain tumors were given intravenous injection of uranyl nitrate at doses of 0.097, 0.12, 0.07, 0.17 and 0.28 mg uranium per kg body wt. Those with the 3 higher doses had elevated urinary catalase and albumin, as well as nonprotein nitrogen, indicating renal toxicity. Other tests failed to show other evidence of toxicity. The authors concluded: "Of the common laboratory animals, man appears to correspond most closely to the rat in regard to intravenous tolerance to uranium."

Model results of kidney burdens from uranium intakes. J Chen, DP Meyerhof and BL Tracy, *Health Physics* **86(1)**, 3-11, 2004. This study uses ICRP models to assess kidney burdens from common intake sources. Calculations were made for 4 age groups from infant to adult. The model predicts kidney burden will be 6.6% of daily intake. Inhaled U compounds of type F and M generally result in higher kidney burdens relative to ingestion of the same compounds.

The distribution and excretion of hexavalent uranium in man. EG Struxness, AJ Luessenhop, SR Bernard and JC Gallimore, *Proceeding of the International Conference on the Peaceful Uses of Atomic Energy*, **Vol 10**, pp. 186-196, United Nations, New York, 1955. (Not Reviewed).

The general pharmacology of heavy metals. H Passow, A Rothstein, TW Clarkson, *Pharmacological Reviews* **13**, 185-224, 1961. This is a comprehensive review of the biochemical and physiological consequences of heavy metal poisoning, although dated, including uranium, mercury, silver and lead. It describes studies of the inhibition of several enzymes by uranyl ion, in addition to interactions of uranyl with cell membranes, affecting cellular transport processes. It also discusses binding to the phosphoryl groups, and binding to RNA. There is extensive review of physiological effects in animals, although the review by Leggett in 1989 is more up to date on this.

Morphologic changes in uranyl nitrate-induced acute renal failure in saline- and water-drinking rats. D.P. Haley, *Laboratory Investigation* **46(2)**, 196-208, 1982. Describes the sequential changes in renal morphology over 5 days following a 10 mg/kg subcutaneous dose of uranyl nitrate using light microscopy and transmission electron microscopy. Within hours the proximal tubules showed loss of brush border and increased vacuolization and necrosis by 5 days. There was little or no evidence of regeneration within 5 days.

The long-term effects of uranyl nitrate on the structure and function of the rat kidney. D.P. Haley, R.E. Bulger, D.C. Dobyan, *Virchows Archiv B [Cell Pathol]* **41**, 181-192, 1982. Studied long-term effects of subcutaneous uranyl nitrate (10 mg/kg), showing acute tubular necrosis. Most injured proximal tubules regenerated by 8 weeks, although some microcysts persisted. There appears to be persistent injury to the kidneys of rats as long as 8 weeks after an acute toxic dose.

Renal tubular fine structure studied during reaction of acute uranium injury. Stone, R.S., Benscome, S.A., Latta, H. and Madden, S.C. *Archives of Pathology* **71**, 160-174, 1961. Acute uranium poisoning (14.4 mg/kg, subcut.) in rats exhibited enlargement of the sub-basilar compartments in proximal, distal and collecting tubules. There was apical swelling and vacuolization in the first 2 days after treatment, at the time polyuria is developing. Necrotic debris appears in the tubular lumen, which appears to be due to tubular resorption of lumen material. Necrosis was extensive in the proximal tubules following loss of microvilli of brush border membrane and swelling of mitochondria and endoplasmic reticulum.

Acute tubular and glomerular lesions in rat kidneys after uranium injury. SA Benscome, RS Stone, H Latta and SC Madden, *Archives of Pathology* **69**, 122-128, 1960. (Not reviewed yet)

Reversible uranyl fluoride nephrotoxicity in the Long Evans rat. G.L. Diamond, P.E. Morrow, B.J. Panner, R.M. Gelein, R.B. Baggs, *Fundamental and Applied Toxicology* **13**, 65-78, 1989. Rats received multiple i.p. injections of 0.66 or 1.32 mg U/kg body wt as uranyl fluoride. Renal tubular injury was evident when renal U levels were 0.7 and 1.4 microg U/g kidney, and was more severe at higher kidney burdens of U (3.4 and 5.6 microg U/g kidney). Complete restoration of kidney damage was observed within 35 days after U exposure, as measured by urinary excretion of glucose, amino acids and protein. The duration of renal injury in this study was much shorter than observed by others (e.g., Haley et al, 1982, above).

Uranyl nitrate induced glomerular basement membrane alterations in rabbits: a quantitative analysis. McDonald-Taylor, Bhatnagar, M.K., Gilman, A., Yagminas, A. and C.K., Singh, A. *Bulletin of Environmental Contamination and Toxicology* **48**, 367-373, 1992. Uranyl nitrate (24 or 600 mg/L) in drinking water for 91 days caused a dose dependent increase in glomerular basement membrane thickness with little or no sign of recovery (i.e., return to normal thickness) over 91 days with clean drinking water.

Increased urinary excretion of basement membrane-like glycoprotein in acute uranium nephropathy. Griswold, W.R. and McIntosh, R.M. *Experientia* **29(5)**, 575-576, 1973. Uranium poisoning was associated with a 50% increase in excretion of major urinary glycoprotein in rat, which may be a reflection of damage to glomerular basement membrane (see above ref).

Effects of uranium on rabbit renal tubules. Bowman, F.J. and Foulkes, E.C. *Toxicology and Applied Pharmacology* **16**, 391-399, 1970. Uranyl acetate (0.2 mg U/kg body wt, i.v.) in rabbit showed damage not only to the proximal renal tubules, but to more distal regions as well, as measured by sodium and water resorption. Potassium secretion by distal tubules was not affected.

Some effects of uranyl acetate on proximal tubular function in rabbit kidney. Nomiya, K. and Foulkes, E.C. *Toxicology and Applied Pharmacology* **13**, 89-98, 1968. Uranyl acetate (0.2 mg/kg) poisoned rabbits had decreased inulin, creatinine and mannitol clearances, implicating back-diffusion of tubular contents as a cause of decreased glomerular filtration rate, according to the authors. Cytotoxic effects on renal tubules impaired tubular function much more than glomerular function.

Foulkes, E.C. Glomerular filtration and renal plasma flow in uranium poisoned rabbits. *Toxicology and Applied Pharmacology* **20**, 380-385, 1971. Uranyl nitrate (0.2 mg/kg) in rabbits did not alter intrarenal volume or distribution of inulin, indicating back diffusion of filtered inulin across damaged tubular epithelium would not be significant. There was no change in glomerular permeability. Decreased tubular transport of p-aminohippurate in the previous paper (Nomiya and Foulkes) would suggest a direct action of uranium on tubular cells.

Aggregation of renal brush border membranes by concanavalin A and heavy metals. Kirschbaum, B.B. *Toxicology and Applied Pharmacology* **64**, 10-19, 1982. Isolated brush border membrane vesicles aggregated in the presence of several heavy metal ions, with La(III) the most effective, followed by Pb(II), Fe(II/III), Cr(III), Sn(II), uranyl, Cd(II) and Hg(II).

Transient proteinuria and aminoaciduria in rodents following uranium intoxication. Bentley, K.W., Stockwell, D.R., Britt, K.A. and Kerr, C.B. *Bulletin of Environmental Contamination and Toxicology* **34**, 407-416, 1985. Female rats were given a parenteral (not specified where) dose of either natural uranyl nitrate or enriched (93% U-235) uranyl nitrate, both in citrate buffer, pH 4.2. Residual tissue burden half times were estimated from data collected on rats sacrificed over 21 days. Kidney showed fast and slow retention half-time components of 2.3 and 13 days, although there was little change in kidney concentration of U between 5 and 21 days, and kidney burden remained at >5% of dose after 21 d. Bone was reported to have 21 day half-time, although there was little change in bone concentration over the 21 days, remaining at nearly 5% of dose at day 21.

Nephrotoxic limit and annual limit on intake for natural U. S. Lu, F.Y. Zhao, *Health Physics* **58**, 619-623, 1990. Describes an industrial accident where a worker, wearing protective clothing, gloves and a gauze mask, was exposed to high levels of UF<sub>4</sub> dust (powder). Urinary U increased from 68 microg/day in the first 24 hr, to about 2000 microg/d at 60 days after the accident and returned to normal about 1000 days later. Kidney damage appeared about 78 days after the accident and appeared to remain for more than 1700 days, as evidenced by high levels of urinary protein excretion, although the authors claim kidney damage “disappeared a short time later.”

Studies on the mechanism of oliguria in a model of unilateral acute renal failure. Cox, J.W., Baehler, R.W., Sharma, H., O’Dorisio, T., Osgood, R.W., Stein, J.H. and Ferris, T.F. *J. Clin. Invest.* **53**, 1546-1558, 1974.

Intracellular behaviour of uranium(VI) on renal epithelial cell in culture (LLC-PK<sub>1</sub>): influence of uranium speciation. H. Mirto, M.H. Hengé-Napoli, R. Gibert, E. Ansoborlo, M. Fournier, and J. Cambar, *Toxicology Letters* **104**, 249-256, 1999. Used this kidney cell line in culture to study uranium toxicity to kidney tubule epithelium. Uranyl bicarbonate, but not uranyl citrate, entered cells and precipitated in the cytoplasmic compartment as uranyl phosphate crystals.

Uranyl nitrate: 28-day and 91-day toxicity studies in the Sprague-Dawley rat. A.P. Gilman, D.C. Villeneuve, V.E. Secours, A.P. Yagminas, B.L. Tracy, J.M. Quinn, V.E. Valli, R.J. Willes, M.A. Moss, *Toxicological Sciences* **41**, 117-128, 1998. This study attempted to establish a no-observed-adverse-effect-level (NOAEL) in rats, but the lowest dose of 0.96 mg uranyl nitrate per liter of drinking water resulted in renal tubular lesions and other pathological effects. Several physical and biochemical parameters were measured, as well as U retention in bones and several soft tissues.

Uranyl nitrate: 91-day toxicity studies in the New Zealand white rabbit. A.P. Gilman, D.C. Villeneuve, B.E. Secours, A.P. Yagminas, B.L. Tracy, J.M. Quinn, V.E. Valli, M.A. Moss, *Toxicological Sciences* **41**, 129-137, 1998. This study attempted to establish a lowest-observed-adverse-effect-level (LOAEL) in rabbits. The lowest dose of 0.96 mg uranyl nitrate per liter of drinking water resulted in renal tubular lesions in males, but the LOAEL for females was higher at 4.8 mg uranyl nitrate per liter. Several physical and biochemical parameters were measured, as well as U retention in bones and kidney.

Uranyl nitrate: 91-day exposure and recovery studies in the male New Zealand white rabbit. A.P.

Gilman, M.A. Moss, D.C. Villeneuve, V.E. Secours, A.P. Yagminas, B.L. Tracy, J.M. Quinn, G. Long, V.E. Valli, *Toxicological Sciences* **41**, 138-151, 1998. This study looked at reversibility of uranyl nitrate-induced renal damage over time. The rabbits in this study required higher doses for lowest-observable-adverse-effect-level than in the previous study (24 mg uranyl nitrate per liter of drinking water) and those in the higher dose group did not show consistent recovery over 91 days after the 91-day exposure. It is proposed that pathogens may have had an adverse effect on U retention and toxicity, since this study used specific-pathogen-free animals.

Effects of oxygen free radical scavengers on uranium-induced acute renal failure in rats. A. Kato, A. Hishida, T. Nakajima, *Free Radical Biology and Medicine* **16(6)**, 855-859, 1994. Subcutaneous injections of superoxide dismutase had no effect on uranyl-induced renal damage, but intraperitoneal (i.p.) injections of dimethylthiourea (DMTU) had a protective effect and dimethylsulfoxide (DMSO) had less of a protective effect.

Role of intrinsic antioxidant enzymes in renal oxidant injury. Yoshioka, T., Bills, T., Moore-Jarrett, T., Greene, H.L., Burr, I.M. and Ichikawa, I. *Kidney International* **38**, 282-288, 1990. Rats were subject to complete renal ischemia for 30 min/day for 3 days or 6 days, which elevated superoxide dismutase (total and cyanide sensitive MnSOD), glutathione peroxidase and catalase by more than 2 fold in the 6 day animals relative to controls. infusion of hydrogen peroxide in the left renal artery resulted in large increase in urinary protein excretion. This paper is mentioned as a reference for factors to consider in renal uranium toxicity that may be mediated by reactive oxygen species, as well as by other chemical or biochemical mechanisms.

Inhibition by uranyl nitrate of adenosine triphosphatases derived from animal and human tissues. BR Nechay, JD Thompson, JP Saunders, *Toxicology and Applied Pharmacology*, **53**, 410-419, 1980. The ATPases studied are important in maintaining ion gradients in all cells and electrolyte balance in the kidney. Uranyl ion inhibits the Na/K ATPase (sodium-potassium pump) 50% at a concentration around 20 microM (about 5 mg/L or per kg tissue). This is a relatively high concentration, but there is about 20% inhibition at 1/10th this level.

The stages in calcification of the rat kidney after the administration of uranium nitrate. LK Dahl, *Journal of Experimental Medicine*, **97**, 681-693, 1953. This study shows that uranyl nitrate induced damage to renal tubules results in calcium deposition in the renal proximal tubules as an early event. The calcium seems to be bound to something other than phosphate in these deposits.

The biphasic nature of renal calcification. LK Dahl, VP Dole, *Journal of Experimental Medicine*, **95**, 341-346, 1952. This study shows that renal calcification induced by uranyl nitrate begins with calcium association with anions other than phosphate, followed by conversion to a calcium phosphate complex.

A study of Ca<sup>2+</sup> metabolism in kidney mitochondria during acute uranium intoxication. E Carafoli, R Tiozzo, I Pasquali-Ronchetti, R Laschi, *Laboratory Investigation*, **25(6)**, 516-527, 1971. Found a large (up to 10 fold increase) accumulation of calcium and phosphate in kidney mitochondria following uranium treatment. It is proposed that calcium is deposited in the mitochondria as an insoluble phosphate complex, which appears in electron micrographs. The energy-dependent Ca uptake process is different from normal kidney mitochondria. There were no changes in calcium or phosphate in endoplasmic reticulum. The uranyl treatment also affected respiration by kidney mitochondria.

Disturbances in electrolyte transport before the onset of uranyl acetate-induced renal failure. T Tyrakowski, J Knapowski, K Baczyk, *Kidney International*, **10**, S144-S152, 1976. This study used

frog skin as a model system to study uranium effects on sodium transport and electrolyte balance. It was found that higher concentrations (2.6 mM) of uranyl acetate affected sodium flux across membranes, but the discussion tends to be mostly about effects in kidney.

In vitro inhibition of Na-K-ATPase by trace metals: relation to renal and cardiovascular damage. HJ Kramer, HC Gonick, E Lu, *Nephron*, **44**, 329-336, 1986. This study showed that heavy metals inhibited the sodium potassium pump from rat kidneys, with 50% inhibition at 3 microM mercury, 70 microM lead, 0.1 mM cadmium and 0.2 mM uranium, the latter similar to the level of inhibition in human kidney found by Nechay et al. (1980). It should be pointed out that the enzyme (Na/K ATPase) assay was performed in crude tissue homogenates, which contain many components that can bind to the metal ions, making less metal ion available for inhibition.

Uranium in urine - normalization to creatinine. Z Karpas, A Lorber, E Elish, P Marcus, Y Roiz, R Marko, R Kol, D Brikner, L Halicz, *Health Physics*, **74(1)**, 86-90, 1998. This study was done to show that diurnal variations in uranium excretion correlate well with diurnal variations in urinary creatinine, and suggests that spot sampling of urine for uranium could be reasonably reliable if measured in relation to creatinine.

Urinary excretion of amino acids by men absorbing heavy metals. TW Clarkson, JE Kench, *Biochemical Journal*, **62**, 361-372, 1956. This study showed that uranium and cadmium induced greater changes in amino acid excretion than lead or mercury. This paper was to be the first part in a series of studies on heavy metal toxicities.

Aminoaciduria in uranium poisoning. Rothstein, A. and Berke, H. *Journal of Pharmacology and Experimental Therapeutics* **96**, 179-187, 1949. Found that amino acid nitrogen in urine correlated better with creatinine than with urine volume. Uranyl nitrate (i.v.) in rabbits resulted in an increase in urinary amino acid nitrogen and its ratio to creatinine; the ratio increased from 0.29 to 1.65 with U treatment.

Glomerular endothelial cells in uranyl nitrate-induced acute renal failure in rats. Avasthi, P.S., Evan, A.P., Hay, D. *Journal of Clinical Investigation* **65**, 121-127, 1980. Uranyl nitrate-induced (15 mg/kg) acute renal failure in rats caused decreased glomerular ultrafiltration. Sodium loaded rats did not show altered renal function after U treatment. It is suggested that U causes alterations in endothelial cells resulting in reduced glomerular ultrafiltration.

The mechanism of acute renal failure after uranyl nitrate. Blantz, R.C. *Journal of Clinical Investigation* **55**, 621-635, 1975. Glomerular filtration rate was reduced to 47% of control by 15 mg/kg uranyl nitrate and to 21% of control by 25 mg/kg dose. Comparing the simultaneous nephron filtration rate at each dose suggests that tubular back-diffusion of solute through damaged tubular epithelium is at least partially responsible for the acute kidney failure and that reduction of the simultaneous nephron filtration rate due to reduced glomerular permeability also contributes to renal failure.

Functional basis for the glomerular alterations in uranyl nitrate acute renal failure. RC Blantz, JC Pelayo, LC Gushwa, R Myers and AP Evans, *Kidney International* **228**, 733-743, 1985 (Not reviewed yet).

Uranyl nitrate-induced acute renal failure in the rat: micropuncture and hemodynamic studies. Flamenbaum, W., Hamburger, R.J., McNeil, J.S. and Huddleston, *Kidney International* **6**, 408-418, 1974. Rats given acute dose of uranyl nitrate (10 mg U/kg body wt, subcut) caused acute renal failure

resulting in renal blood flow rate and glomerular filtration rate (GFR) decreasing to 64% and 67%, resp. Results indicate that dec. GFR is probably not due to tubular obstruction. There were signs of patchy renal cortical ischemia. It is suggested that altered renal hemodynamics were responsible for U-induced renal failure.

Experimental acute renal failure induced by uranyl nitrate in the dog. Flamenbaum, W., McNeil, J.S., Kotchen, T.A. and Saladino, A.J. *Circulation Research* **31**, 682-298, 1972. Uranyl nitrate (10 mg/kg, i.v.) caused reduced inulin clearance (to 25%) and total renal blood flow (to 52%) by 6 hr post-injection. Renal cortex flow decreased to about 65% at 3 hr, but outer medullary flow increased by about 50%, indicating a redistribution of blood flow in the kidney. Plasma renin was 3 fold higher in U-treated vs controls and remained elevated. There was minimal tubular damage by 6 hr as measured histologically, but widespread damage by 96 hr.

The initiation phase of experimental acute renal failure: an evaluation of uranyl nitrate-induced acute renal failure in the rat. Flamenbaum, W., Huddleston, M.L., Hamburger, R.J., Kaufman, J., McNeil, J.S., Schwartz, J.H. and Nagle, R. *Kidney International* **10**, S115-S122, 1976. This paper discusses possible mechanisms for early phase of acute renal failure. Early lack of increased intratubular hydrostatic pressure and absence of intratubular casts would preclude increased hydrostatic pressure as a cause of decreased glomerular filtration rate. Rather decreased GFR may be due to decreased glomerular capillary hydrostatic pressure in the initiation phase.

Microscopic and autoradiographic studies of distribution of uranium in the rat kidney. Jones, E.S. *Health Physics* **12**, 1437-1451, 1966. Rats were injected (i.v.) with varying doses of U as uranyl nitrate and sacrificed at varying times from 1 day to 28 days. Doses ranged from 1 microg/kg to 1000 microg/kg body wt. Higher doses of U result in higher retention in the kidney, with retention ratio of 1.3 for ave. concentration in cortex vs entire kidney. Proximal tubules showed damage at early times (1 day) post injection, while distal tubules showed damage at later times.

Renal hemodynamics in uranyl acetate-induced acute renal failure of rabbits. Sudo, M., Honda, N., Hishida, A., Nagase, M. *Kidney International* **11**, 35-43, 1977. After 2 mg/kg (i.v.) dose of uranyl acetate in rabbit, renal blood flow and creatinine clearance decreased by 60% and 20%, resp, while urine output increased to 2 to 3 times that of controls. Different degrees of recovery and regeneration of damaged tubular cells are discussed. Some animals showed recovery, while others did not.

Glomerular alterations in uranyl acetate-induced acute renal failure in rabbits. S. Kobayashi, M. Nagase, N. Honda and A. Hishida, *Kidney International* **26**, 808-815, 1984. At 15 hr after uranyl acetate treatment, creatinine clearance decreased to 55% of control level. After 5 days, creatinine clearance and urine flow were nearly zero. Morphological changes in glomeruli were observed, which reverted back to normal by 14 days, with recovery of glomerular function.

Influence of uranyl nitrate upon tubular reabsorption and glomerular filtration in blood perfused isolated dog kidneys. Nizet, A. *Pflügers Archiv* [European Journal of Physiology] **391**, 296-300, 1981. Intrarenal venous pressure rose with uranyl treatment, suggesting an increase in proximal tubular hydrostatic pressure caused by decreased glomerular filtration rate. Tubular "back-leak" or back diffusion were excluded.

Intrarenal renin, angiotensin II, and plasma renin in rats with uranyl nitrate-induced and glycerol-induced acute renal failure. F.A.O. Mendelsohn, E.A. Smith, *Kidney International* **17**, 465-472, 1980. Found intrarenal angiotensin II and plasma renin activity were elevated at 6 and 18 hr after acute

uranyl nitrate dose (10 mg/kg, i.p.). The rats had elevated urine flow, sodium excretion, plasma creatinine and impaired creatinine clearance. Kidney renin concentration did not differ from controls (no U). Found that intrarenal angiotensin was not associated with plasma renin activity.

Mechanism of increased renal prostaglandin E2 in uranyl nitrate-induced acute renal failure. Chaudhari, A. and Kirschenbaum, M.A. *Prostaglandins* **26(5)**, 689-699, 1983. There were no changes in rates of synthesis of PGE2 and PGF2a in renal cortex after 1 or 3 days following an acute dose of uranyl nitrate (5 mg/kg), whereas synthesis of PGE2 in the renal medulla decreased by 47% at 1 day and 43% at 3 days. Cortical activity of PGE2-9-ketoreductase decreased by 36% and 76% at days 1 and 3, resp, resulting in a 5 fold increase in cortical tissue levels of PGE2. It is suggested that increased PGE2 may be responsible for return of renal blood flow after 3 days because of its vasodilatory effect.

Renal toxicity in uranium mill workers. M.J. Thun, D.B. Baker, K. Steenland, A.B. Smith, W. Halperin, T. Berl, *Scandinavian Journal of Work and Environmental Health* **11**, 83-90, 1985. This study compared renal tubular function in 39 uranium mill workers and 36 cement plant workers of equivalent age, sex and race. Uranium workers had elevated beta-2-microglobulin and several amino acids relative to the cement workers, indicating renal tubular dysfunction in the uranium workers.

Stimulation of renal organic base transport by uranyl nitrate. Hirsch, G.H. *Canadian Journal of Physiology and Pharmacology* **50**, 533-438, 1972. Uranyl nitrate (6, 1 or 0.5 mg/kg) in rats caused enhanced N-methylnicotinamide and tetraethylammonium (only at 6 mg/kg) uptake by renal cortex slices at 24 and 48 hr after injection. It is stated that nephrotoxicity produced by uranyl nitrate was not directly related to induction of organic base transport, although the mechanism of base transport induction was not known.

The stimulation of Na<sup>+</sup> uptake in frog skin by uranyl ions. W Zeiske, *Biochimica Biophysica Acta* **509**, 218-229, 1978. This study shows that uranyl ion increases membrane permeability to sodium ions. It is suggested that uranyl association with membrane phosphate groups may affect proteins that are responsible for sodium conductance through the membrane. Frog skin has some physiological similarities to mammalian renal tubules.

Disturbances in electrolyte transport in UO<sub>2</sub><sup>2+</sup> ion intoxication - model studies on preliminary stage of toxic acute renal failure. I. The effect of uranyl acetate-induced epithelial tissue in vitro. Tyrakowski, T. *Acta Medica Polona* **20**, 297-306, 1979. Sodium transport was stimulated by presence of 0.03 mM uranyl in the slightly acidic bathing medium on the outer side of frog skin, but inhibited by 2.6 mM uranyl. These effects were not seen at neutral pH. It is suggested that uranyl toxicity may be related to phase changes in cell membrane permeability.

Uranyl nitrate and HgCl<sub>2</sub>-induced alterations in ion transport. Schwartz, J.H. and Flamenbaum, W. *Kidney International* **10**, S123-S127, 1976. This study with turtle bladders suggests that uranyl ion inhibits Na transport by decreasing Na entry into epithelial cells from the mucosal side of the membrane through U (and Hg) binding to membrane constituents. There were no changes in electrical resistance across epithelium nor in passive fluxes of Na or Cl, and the inhibitory effect can be reversed by dithiothreitol (for both metals). (see next article)

Heavy metal induced alterations in ion transport by turtle urinary bladder. JH Schwartz, W Flamenbaum, *American Journal of Physiology*, **230(6)**, 1582-1589, 1976. Found that uranyl nitrate inhibits sodium transport in the turtle bladder. The uranyl ions appeared to remain on the outer surface

of the cells and does not seem to accumulate inside the epithelial cells of the bladder, although the methods used did not attempt to measure uranium inside cells.

Nephrotoxicity of uranyl fluoride in uninephrectomized and sham-operated rats. RK Zalups, RM Gelein, PE Morrow, GL Diamond, *Toxicology and Applied Pharmacology*, **94**, 11-22, 1988. For some reason, one kidney was removed from rats prior to uranium treatment, but treatment with uranyl fluoride induced similar damage to the renal proximal tubules as with rats with both kidneys. They got the idea from a study that looked at mercury toxicity in rats with one kidney.

The enzyme of renal origin in urine as indicators of nephrotoxicity. WE Stroo, JB Hook, *Toxicology and Applied Pharmacology*, **39**, 423-434, 1977. This does not discuss uranium, but discusses other heavy metal nephrotoxins and the measurable parameters of renal toxicity.

## **6] Whole Organism Toxicity and Biosorption**

Cancer risk from the lifetime intake of Ra and U isotopes. C.W. Mays, R.E. Rowland, A.F. Stehney, *Health Physics* **48**, 635-647, 1985. This paper estimates lifetime risk of cancer, particularly bone sarcomas, for people ingesting 5 pCi U per day would be 1.5 per million people. These estimates are based on low absorption of U from the digestive tract, its estimated high rate of excretion and ignores the bystander effect of alpha radiation that was discovered several years after this was published.

Fractional absorption of ingested uranium in humans. Leggett, R.W. and Harrison, J.D., *Health Physics* **68**, 484-498, 1995. Data on the gastrointestinal absorption of ingested uranium is reviewed and analyzed. The ICRP has changed its factor for U uptake from 0.01% in 1959 to 1.0% in 1964 and then to 5% in 1979. This paper discusses uptake from food vs water and uptake of various forms of U (different U compounds). It seems uptake would be higher from drinking water than from food because some food products would contain substances that bind U and decrease its bioavailability or absorption from the gut.

Some quantitative studies of the localization of uranium in the principal organs of rabbits during the course of uranium intoxication by the use of the magneto-optic method. Jones, H.D. and Goslin, R. *American Journal of Physiology* **105**, 693-696, 1933. This early paper used the magneto-optic technique to measure uranium in several organs of rabbits (after sacrifice and ashing) over a period of hours after an acute dose (0.5 mg/kg, subcutaneous). Blood uranium peaked in the first hour, liver and kidney U in the third hour, with a second peak in kidney U in the 6<sup>th</sup> hr. High levels of U appeared in urine in the 4<sup>th</sup> hr and persisted throughout the 24 hr period.

The metabolism of uranium-233 in mice. Kisielecki, W., Faraghan, W.G., Norris, W.P. and Arnold, J.S. *Journal of Pharmacology and Experimental Therapeutics* **104**, 459-467, 1952. Injection of low doses (0.05 and 0.005 microCi) in vein of mice showed 60 percent of dose retained after 1 day, with the majority of retained U-233 in kidney (50%) and other soft tissue, and less in bone (femur, 1%). After 120 days, about 15% of the dose remained in the body, with large decreases in kidney and soft tissue concentrations and small changes in femur concentrations.

Metabolism and sites of effect of uranium after incorporation along different routes in mice, rabbit and piglets. Walinder, G. *Radiation Protection Dosimetry* **26**, 89-95, 1989. Uranium was administered by several different routes (i.v. injection of uranyl salts, inhalation of oxide, cutaneous and subcutaneous deposition of uranyl acetate and U<sub>3</sub>O<sub>8</sub>). Distribution of U in several tissues was measured by whole body autoradiography and histopathological observations. U is rapidly distributed to spleen and bone

surfaces, as well as kidney and liver. U was still detectable in spleen and bone 6 months after injection, but not in liver or kidney. The results presented here imply that large doses of U affect mainly the kidney, whereas low doses or slowly incorporated doses affect mainly spleen and bone surfaces.

Percutaneous absorption of uranium compounds. BM de Rey, HE Lanfranchi, RL Cabrini, *Environmental Research* **30**, 480-491, 1983. Compared topical applications of uranyl nitrate (UN), uranyl acetate (UA), ammonium uranyl tricarbonate (AUT) and ammonium diuranate (ADU) in oil-water emulsions and found UN and AUT are absorbed across the skin of rats, resulting in death within 5 days of daily applications, whereas UA and ADU were absorbed more slowly and hence were less toxic when applied topically, although 60% of uranyl acetate treated animals died within 2 days after the last application (14 days). After AN and AUT application, dense deposits of uranium were observed in intercellular spaces and also scattered in the cytoplasm and nucleus within hours.

Metabolism of ingested U and Ra. M.E. Wrenn, P.W. Durbin, B. Howard, J. Pipsztein, J. Rundo, and D.L. Willis, *Health Physics* **48**, 601-633, 1985. Review the literature and discuss absorption, distribution and elimination of consumed U and recommend <100 :g/L in drinking water to limit toxic effects of U to kidney.

Uranium in humans. I.M. Fisenne, P.M. Perry, N.H. Harley, *Radiation Protection Dosimetry* **24(1/4)**, 127-131, 1988. This report presents data on measurements of uranium in humans from background and high natural activity areas in 12 countries. The paper presents data, with few conclusions drawn.

Uranium and 226-Ra in human bone from Russia. I.M. Fisenne, H.W. Keller, P.M. Perry, *Health Physics* **46(2)**, 438-440, 1984. Five bone types from 6 residents of Moscow were analyzed for radionuclides in bone ash by alpha spectrometry as part of a 26 nation study.

A five-year inhalation study with natural uranium dioxide (UO<sub>2</sub>) dust - I. retention and biologic effect in the monkey, dog and rat. L.J. Leach, E.A. Maynard, H.C. Hodge, J.K. Scott, C.L. Yuile, G.E. Sylvester and H.B. Wilson, *Health Physics* **18**, 599-612, 1970. Found >90% of U retained in body in lungs and tracheobronchial lymph nodes. No evidence of U toxicity related to body weight or mortality. Kidney damage did not occur. Some fibrotic changes suggestive of radiation injury was observed in lymph of dogs and monkeys and in monkey lungs after more than 3 years. Implies minor risk from exposure to UO<sub>2</sub> dust.

A five-year inhalation study with natural uranium dioxide (UO<sub>2</sub>) dust - II. postexposure retention and biological effects in the monkey, dog and rat. L.J. Leach, C.L. Yuile, H.C. Hodge, G.E. Sylvester, H.B. Wilson, *Health Physics* **25**, 239-258, 1973. This is a continuation of the previous reported study, in which a high percentage of dogs developed pulmonary neoplasia 2 to 6 years after exposure. Pulmonary and tracheobronchial lymph node fibrosis (apparently dose dependent) was more pronounced in monkeys than in dogs. The authors indicate no evidence of uranium toxicity was found in records of body weight, mortality, hematologic parameters or histologic inspection of the kidney.

Long-term clearance of inhaled UO<sub>2</sub> particles from the pulmonary region of the rat. Morris, K.J., Khanna, P. and Batchelor, A.L. *Health Physics* **58**, 477-485, 1990. Rats were exposed for 100 min (single exposure) to highly enriched (92.8% U235) UO<sub>2</sub> particles ranging from 2.7 to 3.2 micron diameter and killed at several time points ranging from 1 day to 720 days after exposure. At 720 days, 82% of the total remaining body burden was in the lung and 10% in the thoracic lymph nodes, representing 17% and 2% of the original lung burden at 5 days after inhalation, as measured by whole body gamma scintillation counting. The estimated clearance half time was 247 days. Total mean accumulated alpha particle dosage at 720 days post-inhalation resulted in an estimated 5.7 Gy over the

whole lung. Histological investigation of lungs at 720 days showed widespread lung disease. Relatively little lung damage or disease was found at 180, 360 and 540 days post-inhalation.

Acute toxicity of uranium in rats and mice. JL Domingo, JM Llobet, JM Tomas, J Corbella, *Bulletin of Environmental Contamination and Toxicology* **39**, 168-174, 1987. The study found oral LD50 was 204 mg/kg for rats, and 242 mg/kg for mice. The subcutaneous LD50 was 8.3 mg/kg for rats and 20.4 mg/kg for mice.

The distribution and retention of hexavalent <sup>233</sup>-U in the beagle. W. Stevens, F.W. Bruenger, D.R. Atherton, J.M. Smith, G.N. Taylor, *Radiation Research* **83**, 109-126, 1980. Seven beagles were injected with 3 mg U/dog and sacrificed at different time points from 1 to 726 days post-injection. Up to 60% of the U was excreted in the first day, primarily in the urine. Whole body retention was 17% at 17 days, 10% at 94 days, 7.6% at 1 yr and 5% at 2 yr. At 1 day 22% of injected dose was found in kidney (of 1 dog), with the bulk of the U in the proximal tubules and almost none in the glomeruli. Very little U was deposited in liver. Nearly 8% was deposited in bone, with a gradual decrease over 2 years, at with time only about 4% of the dose remained in the skeleton (although these numbers are for only one animal per time point). [It should be noted that the skeletal data for the animal sacrificed at day 21 was thrown out because it was far below the values for animals sacrificed on days 14 and 94].

Uranium in the tissues of an occupationally exposed individual. R.L. Kathren, J.F. McInroy, R.H. Moore, and S.E. Dietert, *Health Physics* **57**, 17-21, 1989. This group from Hanford and Los Alamos used radiochemical determination to analyze lung, kidney, liver and bone collected at autopsy of a 50 yr old male employed from 1952 to 1978 as a chemical operator in a U processing plant and died of cardiac event at work. The U deposition pattern was 63:2.8:1 in skeleton: liver: kidney. Numerous data are given in the paper over the life of this individual. Authors indicate that in vivo chest counts for this individual indicate long term U-deposition more than twice that estimated from postmortem analysis of lung and associated lymph, and argue that in vivo estimates may be high and therefore conservative from the standpoint of operational radiation protection. They do not indicate any consideration of rib cage contribution to this comparison, suggesting there may be flaws in their model.

Percutaneous toxicity of uranyl nitrate: its effect in terms of exposure area and time. R Lopez, PL Diaz Sylvester, AM Ubios, RL Cabrini, *Health Physics*, **78(4)**, 434-437, 2000. This study used 0.6 g/mL uranyl nitrate in an oil-water emulsion spread on the skin of shaved rats. The skin area exposed (0.5 to 16 cm<sup>2</sup>) and duration of exposure (1 min to 24 hr) were varied. Toxicity was evaluated by microscopic inspection of histological sections of kidney and histomorphometric evaluation of bone. Daily topical application of uranyl nitrate for 3 days resulted in all animals receiving the largest exposures (8 and 16 cm<sup>2</sup>) dying. When duration of exposure with 8 cm<sup>2</sup> area was varied, the survival rate decreased with increasing exposure time, from 100% survival (at the end of 4 days) for 15 min exposure, to 45% survival for 1 hr exposure and 10% survival for 8 hr exposure. This shows that immediate washing with soap and water can prevent the lethal effects of accidental spilling of uranyl nitrate on the skin - a serious concern of uranium industry workers.

Skin alterations induced by long-term exposure to uranium and their effect on permeability. Ubios, A.M., Marzorati, M., Cabrini, R.L. *Health Physics* **72**, 713-716, 1997. Rats received 30 daily topical exposures to U<sub>3</sub>O<sub>8</sub> (12 mg/d). Results show decreased epidermal thickness of U treated rats and increased skin permeability, both at the end of the 30 day treatment or following 60 days of nonexposure. The results indicate marginal recovery in 60 days.

Uranyl action on sugar transport across rat jejunum. Rodriguez-Yoldi, M.J. and Ponz, F. *Revista Española de Fisiología* **42**, 359-364, 1986. Showed uranyl ion inhibits glucose and galactose transport in the rat jejunum, but has weaker effect on fructose transport. Washing tissue with 10 mM EDTA reversed the inhibition only slightly. The inhibition was not immediate, but required several minutes to reach maximum effectiveness.

The effects of cytochrome C and uranyl on the active transport of sugars by the intestine. Ponz, F. and Lluch, M. *Revista Española de Fisiología* **14**, 217-224, 1958. Showed that cyt c can stimulate intestinal absorption of sugars, whereas uranyl ion inhibited intestinal absorption of glucose and galactose, but did not affect fructose absorption.

The biological behavior of  $^{239}\text{PuO}_2$  particles: role of the peritoneal mononuclear phagocyte. C.L. Sanders, *Radiation Research* **38**, 125-139, 1969. Plutonium dioxide particles injected into the peritoneal cavity of rats were phagocytized by mononuclear phagocytes, which accumulated the particles. The average phagocyte engulfed about 500 of the ca. 0.12 micron diameter particles. The Pu-ladened phagocytes accumulated in lymph nodes and the Pu particles were slowly released back into the peritoneal cavity from the lymph.

Mechanism of uranium poisoning. H.C. Hodge, A.M.A. *Archives of Industrial Health* **14**, 43-47, 1956. This early review erroneously indicates when insoluble uranium dusts are inhaled, there is no chemical hazard to the kidneys, although several studies of  $\text{UO}_2$  and  $\text{U}_3\text{O}_8$  inhalation years before this publication showed kidney damage to occur.

Distribution and form of uranium-containing deposits in chickens treated with uranyl nitrate. Mollenhauer, H.H., Harvey, R.B., Kubena, L.F., Droleskey, R.E. and Davis, R. *Veterinary Pathology* **23**, 706-711, 1986. Shows that chicken kidneys are damaged by uranyl nitrate the same way as mammalian kidneys, primarily tubular damage with U deposits in necrotic cells.

Effects of depleted uranium on the health and survival of *Ceriodaphnia dubia* and *Hualella azteca*. W.W. Kuhne, C.A. Caldwell, W.R. Gould, P.R. Fresquez and S. Finger, *Environmental Toxicology and Chemistry* **21**, 2198-2203, 2002. Looked at LC50 (lethal conc for 50% mortality) of DU on survival of *C. dubia* was 10.5 mg/L. Reproductive effects occurred at lowest observable conc of >3.91 mg/L, with no observable effect at 1.97 mg/L. The 14 day LC50 for *H. azteca* was 1.52 mg/L. Authors conclude that the levels needed for toxicity exceeded conc of total U observed in runoff at Los Alamos National Lab and the runoff would not pose a threat to these aquatic invertebrates.

Biosorption of uranium and lead by *Streptomyces longwoodensis*. Friis, N. and Myers-Keith, P. *Biotechnology and Bioengineering* **28**, 21-28, 1986. Studied the effects of metal concentration, pH, cell concentration and culture age on heavy metal sorption by lyophilized cells of title organism. Cells harvested from stationary growth phase exhibited high capacity U uptake (0.44 g U/g dry wt) at pH 5. There was strong preference for uranyl ions over Pb ions. There was a correlation between U uptake and cellular phosphorus content. It is postulated that U binds phosphate residues in the cell wall as well as in the cytoplasm. Optimum pH for U uptake was 4.6.

Microbial cells as biosorbents for heavy metals: accumulation of uranium by *Saccharomyces cerevisiae* and *Pseudomonas aeruginosa*. Strandberg, G.W., Shumate, S.E. and Parrott, J.R. *Applied Environmental Microbiology* **41**, 237-245, 1981. Uranyl ion accumulated on the extracellular surface of *S. cerevisiae* but intracellularly in *P. aeruginosa*, with accumulation by the former influenced by pH, temperature and certain ions, but not in the latter. Metal uptake was not dependent on cell

metabolism. U could be washed from the surface of *S.cerevisiae*, allowing these cells to be reused as sorbent.

Accumulation and cellular distribution of uranium in *Thiobacillus ferrooxidans*. DiSpirito, A.A., Talnagi, J.W. and Tuovinen, O.H. *Archives of Microbiology* **135**, 250-253, 1983. Uranyl uptake by washed cell suspensions was dependent on external U concentration, and was influenced by pH but not transition metals in the medium. Cells inactivated by either UV radiation or potassium cyanide accumulated about 40% more U than viable cells. Most of the U was associated with cell wall and membrane fractions, and relatively little was in cytoplasm or periplasmic space. Cyanide poisoning caused an 8-11 fold increase in cytoplasmic conc of U.

Uranyl nitrate inhibition of transport systems in *Saccharomyces cerevisiae*. Maxwell, W.A., Metzler, R. and Spoerl, E. *Journal of Bacteriology* **105**, 1205-1206, 1971. Uranyl nitrate inhibited transport of maltose, glycine and biotin, indicating inhibition of three distinctly different transport systems by uranyl ion. Glycerol, which is presumed to enter the yeast cell by diffusion, is affected by high concentrations of uranyl in a manner different from other compounds using transporters.

Ultrastructural localization of uranium biosorption in *Penicillium digitatum* by stem x-ray microanalysis. Galun, M., Siegel, S.M., Cannon, M.I., Siegel, B.Z. and Galun, E. *Environmental Pollution* **43**, 209-218, 1987. Fungal cultures incubated with uranyl chloride (1000 or 2000 ppm) for 3, 18 or 24 hr showed significant retention of U following thorough rinsing with distilled water, but was removed by rinsing with alkaline carbonate solutions. Crystalline deposits were observed on the outer surface of hyphal cell wall following short exposures to relatively low U conc, but inside the cell walls following longer exposures and relatively high U conc.

Uranium accumulation in the lichen *Cladonia rangiferina*. Part II. Toxic effects of cationic, neutral and anionic forms of the uranyl ion. Boileau, L.J.R., Nieboer, E., Richardson, D.H.S. *Canadian Journal of Botany* **63**, 390-397, 1985. Uranyl ion toxicity was dependent on speciation. Uranyl oxalate anion complex was more toxic than uncomplexed uranyl cation to photosynthesis in this lichen. No toxic effect was observed from the neutral uranyl phthalate complex. Samples of lichen showing low photosynthetic activity (typical in winter) were affected more. The data suggest that U interferes with bicarbonate transport into the algal cell and blocks carbohydrate transport from algal cell to symbiont.

An all or none response in the release of potassium by yeast cells treated with methylene blue and other basic redox dyes. H Passow, A Rothstein, B Loewenstein, *Journal of General Physiology*, **43**, 97-107, 1959. This paper shows that uranyl ion can protect cells from methylene blue- induced loss of  $K^+$ , perhaps by finding to sites on the cell membrane that bind the cationic dye. Only basic dyes show this effect, not acidic dyes, and only the oxidized form of the dye is effective. It is suggested the dye first binds to RNA in the cell membrane, followed by oxidation of sulfhydryl groups. It is curious that uranyl does not work in the same way, if oxidation of protein sulfhydryl groups is part of the mechanism, since uranyl ion is a good oxidizing agent.

Evaluation of phytotoxicity and genotoxicity of uranyl nitrate in *Allium* assay system. B.B. Panda, K.K. Panda, J. Patra, G.K. Sahu and R.K. Mitra, *Indian Journal of Experimental Biology* **39**, 57-62, 2001. Uranyl nitrate inhibited growth of *Allium cepa* at  $>25 \mu\text{M}$  conc, with uranyl entry into root cells. U failed to induce micronuclei and was neither clastogenic nor aneugenic, but between 25 and 100  $\mu\text{M}$  conc it increased significantly the frequency of sister chromatid exchange vs controls, that possibly interfered with DNA replication and/or repair processes.

## 7] Effects on Reproduction and Development

Reproductive and developmental toxicity of natural and depleted uranium: a review. Jose L. Domingo, *Reproductive Toxicology* **15**, 603-609, 2001. A very good review with 54 refs on uranium exposure causing decreased fertility, embryo/fetal toxicity, including teratogenicity and reduced growth of the offspring. Also discusses the prevention of toxic effects in animals by chelating agents such as ethane-1-hydroxy-1,1-bisphosphonate (EHBP), which is more effective than the classical chelator Tiron (sodium 4,5-dihydroxybenzene-1,3-disulfonate) or diethylenetriamine-pentaacetic acid (DTPA), the latter being least effective.

A review of the effects of uranium and depleted uranium exposure on reproduction and fetal development. Darryl P. Arfsten, Kenneth R. Still and Glenn D. Ritchie, *Toxicology and Industrial Health* **17**, 180-191, 2001. Very different kind of review compared to Domingo's review (above). Discusses genetic mutations and chromosomal aberrations, as well as effects on protein and steroid synthesis. Also mentions U interferes with cyt P450 activity. Mentions decreased reproductivity in animals could be due to effects on parental libido and pup rearing behavior.

The developmental toxicity of uranium in mice. J.L. Domingo, J.L. Paternain, J.M. Llobet, J. Corbella, *Toxicology*, **56**, 143-152, 1989. Treatment of pregnant mice with uranyl acetate resulted in decreased maternal weight gain and food consumption and increased liver weight. There was no change in the number of fetuses or fetal resorptions or dead fetuses, but there were dose related fetal effects, including reduced body weight and body length, and increased skeletal malformations, such as cleft palate, bipartite sternbrae, reduced ossification and ossified skeletal variations. The lowest dosage of uranyl acetate dihydrate was 5 mg/kg, which produced a toxic effect.

Effects of uranium poisoning on cultured preimplantation embryos. M Kundt, AM Ubios, RL Cabrini, *Biological Trace Element Research*, **75**, 235-244, 2000. Cultured mouse embryos were exposed to uranyl nitrate at levels of 26 to 208 microg/mL. Although these are relatively high levels of exposure (it seems), the lowest levels induced delays in embryo development.

Embryotoxicity and teratogenicity of uranium in mice following subcutaneous administration of uranyl acetate. MA Bosque, JL Domingo, JM Llobet, J Corbella, *Biological Trace Element Research* **36**, 109-118, 1993. Multiple injections of uranyl acetate (0.5, 1.0 and 2.0 mg/kg/day) during gestation. Maternal and embryotoxicity occurred at all doses of uranium. The latter as measured by nonviable implantations and postimplantation loss. Teratogenicity was observed at the higher doses (1 and 2 mg/kg).

Influence of chronic exposure to uranium on male reproduction in mice. JM Llobet, JJ Sirvent, A Ortega, JL Dominago, *Fundamental and Applied Toxicology* **16**, 821-829, 1991. Male mice were treated with high doses of uranyl acetate at doses of 0, 10, 20, 40, and 80 mg/kg/day in drinking water for 64 days. Male mice were mated with females for 4 days after treatment. Uranium treated males showed a significant (not dose related) decrease in producing pregnancies. Testicular function was not affected at any dose of uranium, as measured by normal testes and epididymis weights and normal spermatogenesis.

Evaluation of the perinatal and postnatal effects of uranium in mice upon oral administration. JL Domingo, A Ortega, JL Paternain, J Corbella, *Archives of Environmental Health* **44(6)**, 395-398, 1989. Studied effects of uranyl acetate (0, 0.05, 0.5, 5, and 50 mg/kg) administered by gavage from day 13 of gestation until day 21 of lactation. Only the highest dose affected litter size and pup growth.

## 8] Neurological Effects

Uranyl acetate-induced sensorimotor deficit and increased nitric oxide generation in the central nervous system in rats. M.B. Abou-Donia, A.M. Dechkovskaia, L.B. Goldstein, D.U. Shah, S.L. Bullman, W.A. Khan, *Pharmacology, Biochemistry and Behavior* **72**, 881-890, 2002. The study was designed to follow effects of daily injections of 0.1, 1, 10 and 100 mg/kg in rats for 7 days, with an observation period up to 30 days. All rats in the 10 and 100 mg/kg group died before the 7<sup>th</sup> injection. Animals in the lower dose groups survived but showed neurological deficits wrt inclined plane performance, grip time, beam walk score and beam walk time. There were some specific changes in NO in cortex and midbrain of lowest dose group and increased AChE acty in cortex of the 1 mg/kg dose group. These results indicate subtle neurological deficits in relatively low dose U exposure as uranyl acetate.

Electrophysiological changes in hippocampal slices isolated from rats embedded with depleted uranium fragments. T.C. Pellmar, D.O. Keyser, C. Emery and J.B. Hogan, *NeuroToxicology* **20**, 785-792, 1999. Compared implanted DU pellets with Tantalum (Ta) as a control metal, with observations on brain tissue (hippocampus) after 6, 12 and 18 months. After 6 mo. synaptic potential amplitudes were less capable of eliciting spikes (E/S coupling). At 12 mos amplitudes of synaptic potentials were signif. increased in tissue from DU treated rel to Ta treated controls and E/S coupling was reduced. By 18 mos there was no differences between electrophysiol. measurements of DU and Ta treated tissues. Authors suggest that aging and DU exposure converge at 18 mos to obscure the effects of the metal toxicity. Kidney toxicity was not evident in these animals.

Effects of uranyl ions on neuromuscular transmission of chick biventer cervicis muscle. SY Lin-Shiau, WM Fu, CY Lee, *Archive International de Pharmacodynamic*, **241**, 332-343, 1979. At low concentrations (0.04 mM to 0.12 mM) uranyl increased twitch responses to indirect stimulations of muscle. At higher concentrations (0.8 to 1.2 mM) uranyl induced muscle contractions that were antagonized by d-tubocurarine, a nicotinic receptor antagonist. Other evidence suggests the uranyl induced contraction could be due to effects on stimulation of release of acetylcholine. Higher concentrations (2.4 mM) of uranyl block neuromuscular transmission.

Topochemical factors in potentiation of contraction by heavy metal cations. Sandow, A. and Issacson, A. *Journal of General Physiology* **49**, 937-961, 1966. Found that 0.5 microM uranyl ion will potentiate the twitch of frog sartorius and toe muscles by prolonging the active state of contraction, which is rapidly reversed by phosphate ions. It is suggested that U may prolong the action potential. It appears U binds to connective tissue as well as muscle fibers.

## 9] Effects on Bone

Uranium inhibits bone formation in physiologic alveolar bone modeling and remodeling. AM Ubios, MB Guglielmotti, T Steimetz, RL Cabrini, *Environmental Research* **54**, 17-23, 1991. Acute intoxication (2 mg/kg examined after 14 days) and chronic (0.8 mg/kg examined after 14, 30 and 60 days) was induced with <sup>238</sup>U-uranyl nitrate by intraperitoneal injection. The lower jaws were histologically examined and it was found that uranium intoxication resulted in decreased bone formation in addition to an increase in bone resorption at day 14, whereas only bone formation was suppressed on days 30 and 60 in the chronic experiment.

Effects of acute intoxication with uranyl nitrate on bone formation. MB Guglielmotti, AM Ubios, BM

de Rey, RL Cabrini, *Experientia* **40**, 474-476, 1984. This was a histological study of healing sockets following molar extraction in rats that were treated with 2 mg/kg uranyl nitrate vs controls. There was a significant decrease in bone formation and decreased volume density of trabecular bone.

Distribution and excretion of injected uranium. W.F. Neuman, R.W. Fleming, A.L. Dounce, A.B. Carlson, J. O'Leary, B. Mulryan, *Journal of Biological Chemistry* **173**, 737-748, 1948. This was the first report in the public literature (unclassified) that showed bone has a high affinity for uranium. About 20 to 30 percent of a toxic dose of uranium was deposited in bone of male rats within 2.5 hr, and bone accounted for 90% of the uranium retained in the body after 40 days. Although more U was retained in bones of males than females, this was attributed to faster growth rates in the younger males that were the same body weight as females. It was suggested in a later paper (below) that the greater deposition in the younger, faster growing animals was due to greater bone vascularity.

The deposition of uranium in bone: I. Animal studies. W.F. Neuman, M.W. Neuman, B.J. Mulryan, *Journal of Biological Chemistry* **175**, 705-709, 1948. This showed an inverse age dependent deposition of U in bone of rats, with >50 microg U/g bone at 2.5 weeks and <10 microg U/g bone at 15 weeks. Rachitic animals showed a much greater deposition of U than normal rats. These results would indicate that young, growing individuals (of any species), and especially those that may be deficient in calcium due to malnutrition, would be much more susceptible to U retention in bones than adults. It is also discussed that uranyl ion does not appear to displace calcium ion in the hydroxyapatite, rather it appears to be deposited on the surface. The rapid deposition in bone shortly after a toxic dose was much faster than the rate of calcification of bone.

The deposition of uranium in bone: II. Radioautographic studies. M.W. Neuman, W.F. Neuman. *Journal of Biological Chemistry* **175**, 711-714, 1948. Using radioautography, it was shown that U deposited on the surface of mineral portions of the bone, particularly in the vicinity of the vascular system and in areas of active calcification. Once fixed, there was little redistribution. As growth and calcification continued, new bone accumulated over U deposits and there was little resorption of U, unlike calcium resorption that is needed for bone reformation during growth. The lack of U resorption was attributed to the insolubility of the U-impregnated bone material.

The deposition of uranium in bone: III. The effect of diet. W.F. Neuman, M.W. Neuman, E.R. Main, B.J. Mulryan, *Journal of Biological Chemistry* **175**, 715-719, 1948. The effect of acidic, alkaline and rachitogenic diets were studied with regard to U deposition in and mobilization from bone. Diets were made acidic with 0.32% ammonium chloride, or made alkaline with 0.5% sodium bicarbonate; which seems a questionable approach to altering blood pH. The acidic and alkaline diets did not significantly alter the rate of U mobilization from bone. The rachitogenic diet did result in greater mobilization of U from bone, probably due to less bone deposition on top of the U layer, allowing the U to be in equilibrium with body fluids. It is estimated that the half-life of U in bone of normal fed rats was about 50 to 60 days in this study, but this conclusion did not seem to take into consideration different rates of bone growth and age of the animal, which are known to affect U deposition and subsequent overlaying of calcified bone structure.

Uranium in bone: metabolic and autoradiographic studies in the rat. Priest, N.D., Howells, G.R., Green, D. and Haines, J.W. *Human Toxicology* **1**, 97-114, 1982. Approximately one-third of the U-233 (500 Bq) from intravenous injection of uranyl citrate is retained in the skeleton of the rat with a biological half time of about 40 days. The U is deposited on all bones, but preferentially on accreting bones and in calcifying zones of cartilage. Bone accretion results in burial of the U under new layers, while bone resorption removes U from the surface. Resorbed U enters the bloodstream and may be

redeposited in other bones or in soft tissues, or excreted by the kidneys. These authors argue that uranyl behaves like  $\text{Ca}^{2+}$  ion, but this may be a gross generalization only in that both have some affinity for phosphate groups in bone.

The deposition of uranium in bone. Rowland, R.E. and Farnham, J.E. *Health Physics* **17**, 139-144, 1969. Autoradiographic analysis of bone from animals sacrificed between 2 and 72 days after an acute injection of U-232 or U-233 as uranyl nitrate. At 2 days after injection the U was localized on bone surfaces, but by 6 days its distribution was more diffuse and by 72 days there were intense hot spots over the growth regions and diffuse distribution throughout all of the pre-existing bone.

The early distribution of 239-Pu, 241-Am and 233-U in soft tissues and skeleton of old rats. A comparative study. Sontag, W. *Human Toxicology* **2**, 91-100, 1983. Radionuclide activities in soft tissues of male and female rats differed and also varied between 7 days and 28 days. In bones, the 3 radionuclide activities showed subtle differences, except in femor, which had about 50% more Pu than Am or U.

Long-term behaviour of 239-Pu, 241-Am and 233-U in different bones of one-year-old rats, macrodistribution and macrodosimetry. Sontag, W. *Human Toxicology* **3**, 469-483, 1984. Initial skeletal deposition of these elements following i.v. doses were Pu>Am>U. The half time for retention of Pu and Am were much greater than 1 yr, but was 140 days for female and 80 days for male rats.

Physiologically based models for bone-seeking elements: II. kinetics of lead disposition in rats. O'Flaherty, E.J. *Toxicology and Applied Pharmacology* **111**, 313-331, 1991. This paper is included because this toxic heavy metal also binds to bone and the model proposed may be useful for uranium modeling.

## **10] Treatment for Uranium Poisoning - Chelation Therapy and other regimens**

Treatment of experimental acute uranium poisoning by chelating agents. Ortega, A., Domingo, J.L., Gomez, M. and Corbella, J. *Pharmacology and Toxicology* **64**, 247-251, 1989. Tested 16 chelating agents for efficacy as antidotes to uranium poisoning, weighing the relative toxicity of each with its enhancement of survival from a lethal dose of uranyl acetate. Found Tiron, gallic acid and DTPA to be most effective. Tiron and 5-aminosalicylic acid were most effective in increasing the fecal and urinary excretion of uranium, respectively.

Effectiveness of chelation therapy with time after acute uranium intoxication. Domingo, J.L., Ortega, A., Llobet, J.M., Corbella, J. *Fundamental Applied Toxicology* **14**, 88-95, 1990. This study found that Tiron or gallic acid given at 0, 0.25 or 1 hr after acute uranium exposure (uranyl acetate, i.p.) both increased uranium excretion and Tiron decreased kidney and bone burden of U after 4 days (gallic acid significant only when given at 1 hr). Administration of chelating agents at 4 hr or 24 hr after U exposure had no statistically significant effect on either excretion or tissue burden after 4 days.

The effects of repeated parenteral administration of chelating agents on the distribution and excretion of uranium. Domingo, J.L., Ortega, A., Llobet, J.M., Paternain, J.L. and Corbella, J. *Research Commun. in Chemistry, Pathology and Pharmacology* **64**, 161-164, 1989. Found Tiron significantly increased urinary and fecal excretion of uranium and significantly decreased U deposition in liver, spleen and bone in mice. Gallic acid and DTPA decreased U deposition in liver.

Comparative effects of the chelators sodium 4,5-dihydroxybenzene-1,3-disulfonate (Tiron) and

diethylenetriaminepentaacetic acid (DTPA) on acute uranium nephrotoxicity in rats. J.L. Domingo, A. de la Torre, M. Bellés, E. Mayayo, J.M. Llobet, and J. Corbella, *Toxicology* **118**, 49-59, 1997. Tiron was more effective than DTPA in reducing the nephrotoxic effects of uranyl acetate through increasing urea and creatinine excretion, but had little or no ameliorative effect on urine volume, total protein excretion or NAG (N-acetyl- $\beta$ -D-glucosaminidase) excretion.

Phenolic chelating agents as antidotes for acute uranyl acetate intoxication in mice. Basinger, M.A., Forti, R.L., Burka, L.T., Jones, M.M., Mitchell, W.M., Johnson, J.E., Gibbs, S.J. *Journal of Toxicology and Environmental Health* **11**, 237-246, 1983. Compared 9 phenolic chelating agents with DTPA as antidotes for uranium poisoning. Tiron was most effective in decreasing U burden in liver and kidneys and promoting survival in mice. p-Aminosalicylic acid also promoted survival.

Tiron (sodium 4,5-dihydroxybenzene-1,3-disulfonate) as an antidote for acute uranium intoxication in mice. Basinger, M.A. and Jones, M.M. *Research Communications in Chemical Pathology and Pharmacology* **34(2)**, 351-358, 1981. Tiron was much more effective than  $\text{Na}_3\text{CaDTPA}$  as antidote to lethal doses of uranyl acetate (40 or 80 mg/kg) in mice.

Efficacy of Tiron for enhancing the excretion of uranium from the rat. Stradling, G.N., Gray, S.A., Moody, J.C. and Ellender, M. *Human and Experimental Toxicology* **10**, 195-198, 1991. This study used U-233 isotope, which has a high specific radioactivity and injected it into the lung of rats at a dose of 10 microg per rat or about 55 microg/kg body wt - a relatively low dose of uranium, but a high level of radioactivity. High doses of Tiron increased the rate of U excretion and decreased the U burden in whole body and most tissues, except lung. It is argued in the discussion that Tiron only decreases the body burden by 35% and kidney burden by 55%, although there was little or no effect on lung burden and an increase in liver burden of U. The reviewer finds some problems with the protocol in this study.

Polymerization of uranyl-tiron chelates. Gustafson, R.L., Richard, C. and Martell, A.E. *Journal of the American Chemical Society* **82**, 1526-1534, 1960. Below pH 3.5 uranyl ion forms a mononuclear 1:1 complex with tiron. At pH 5.3 a ternuclear complex is formed, indicating polymerization (bridging) by hydroxide ions in solution and is independent of excess tiron concentration. The presence of various hydrolyzed species at various pH values is discussed.

New agents for *in vivo* chelation of uranium (VI): efficacy and toxicity in mice of multidentate catecholate hydroxypyridinonate ligands. Durbin, P.W., Kullgren, B., Xu, J. and Raymond, K.N. *Health Physics* **72**, 865-879, 1997. Authors claim that these agents are the first multidentate ligands found to bind uranyl efficiently at physiological pH, promote its excretion and reduce its deposition in kidney and bones. Several of the 10 tested ligands showed significant reduction in kidney, skeleton and whole body deposition of U following injection (i.p.) of 30 micromol ligand per kg body wt after a 0.4 micromol uranyl chloride (ca. 100 microg U/kg) in mice.

*In vivo* chelation of Am(III), Pu(IV), Np(V) and U(VI) in mice by TREN-(me-3,2-HOPO). Durbin, P.W., Kullgren, B., Xu, J. and Raymond, K.N. *Radiation Protection Dosimetry* **53**, 305-309, 1994. Found title compound to be nearly as effective at removing body burden of Pu(IV) and Am(III), and appears to be less toxic than one of the most effective chelation therapy agents for Pu(IV), 3,4,3-LI(1,2-HOPO) and more effective than the safer chelating agent,  $\text{CaNa}_3\text{DTPA}$ . However, this chelator showed similar effect with DTPA for U chelation.

Lethality due to uranium poisoning is prevented by ethane-1-hydroxy-1,1-bisphosphonate (EHBP).

Ubios, A.M., Braun, E.M. and Cabrini, R.L. *Health Physics* **66**, 540-544, 1994. Injected very young rats (14 g) with uranyl nitrate (2 mg/kg) with or without the U binding ligand EHBP (single dose of 10 mg/kg body wt in saline). Fifty % of animals receiving uranyl nitrate alone died on the 8<sup>th</sup> day, whereas all animals receiving EHBP, either with or without the uranyl dose survived to the end of the experiments (9 days or 60 days). Only one of 17 rats treated with uranyl alone survived to the 60<sup>th</sup> day. There was also structural damage to kidneys of the uranyl (only) treated rats, but structural damage was not seen in those treated with EHBP (with or without uranyl dose), indicating this is an effective and apparently relatively nontoxic chelating agent for treatment of uranium poisoning.

Tetracycline in uranyl nitrate intoxication: its action on renal damage and U retention in bone. Guglielmotti, M.B., Ubios, A.M., Larumbe, J. and Cabrini, R.L. *Health Physics* **57**, 403-405, 1989. This study showed that tetracycline (which binds calcium and interferes with Ca metabolism) was unable to prevent the binding of U to bone and exacerbated U-induced renal injury. The latter effect may have been due to nephrotoxicity of tetracycline which may be augmented by U damage. These results would have important implications for the use of tetracycline and related antibiotics by personnel at risk of high uranium exposures.

Effect of dithiothreitol on mercuric chloride- and uranyl nitrate-induced acute renal failure in the rat. Kleinman, J.G., McNeil, J.S., Hamburger, R.J. and Flamenbaum, W. *Kidney International* **12**, 115-121, 1977. Found that dithiothreitol ameliorates mercury and uranium-induced acute renal failure when administered 30 min after a acute dose of HgCl<sub>2</sub> or uranyl nitrate in rats.

Avidity of folic acid for carcinogenic metal ions, aluminium(III), chromium(III), beryllium(II), lead(II) and uranium(VI). Nayan, R. and Arun, K.D. *Zeitschrift Naturforschung* **25**, 1453-1457, 1970. Folic acid would not be an effective therapeutic agent for metal chelation.

The effects of calcium disodium ethylenediamine tetraacetate on uranium poisoning in rats. Dagirmanjian, R., Maynard, E.A. and Hodge, H.C. *Journal of Pharmacology and Experimental Therapeutics* **117**, 20-28, 1956. Found the LD50 for CaEDTA was about 3850 mg/kg body wt. The 30 day LD50 for uranyl nitrate (i.p.) was 3.2 mg/kg without EDTA, but increased to 9.3 mg/kg when 50 mg CaEDTA (per rat) was administered at 2, 4 and 6 hr after U treatment. CaEDTA increased the 24 hr urinary U excretion. CaEDTA did not mobilize U deposits in the skeleton.

The stimulating influence of sodium citrate on cellular regeneration and repair in the kidney injured by uranium nitrate. Donnelly, G.L. and Holman, R.L. *Journal of Pharmacology and Experimental Therapeutics* **75**, 11-17, 1942. Dogs given 5 mg uranyl nitrate alone showed acute signs of toxicity and 12 of 13 dogs died between 9 and 13 days after uranium treatment. When 230 mg sodium citrate was given (i.v.) each day for 5 d prior and 5 d after U treatment, only 1 dog died and survivors showed little, if any signs of intoxication from the same dose of U. There was also significant tubular regeneration in the citrate treated animals.

The effect of BAL on experimental lead, tungsten, vanadium, uranium, copper and copper-arsenic poisoning. Lusky, L.M., Braun, H.A. and Laug, E.P. *Journal of Industrial Hygiene and Toxicology* **31**, 301-305, 1949. BAL (2,3-dimercaptopropanol) was effective in decreasing lead toxicity and lead deposition in bone, but was ineffective for vanadium or uranium.

Effect of saline loading on uranium-induced acute renal failure in rats. Hishida, A., Yonemura, K., Ohishi, K., Yamada, M. and Honda, N. *Kidney International* **33**, 942-946, 1988. Found that continuous isotonic saline infusion following an acute dose of uranyl acetate (5 mg/kg) resulted in

higher inulin clearance rate, higher urine flow and less intratubular cast formation. The beneficial effect of saline was associated with less cast formation rather than with suppressed renin-angiotensin activity or enhanced urinary U excretion.

Uranyl nitrate-induced acute renal failure in the rat: effect of varying doses and saline loading. Ryan, R., McNeil, J.S., Flamenbaum, W. and Nagel, R. *Proceedings of the Society for Experimental Biology and Medicine* **143**, 289-296, 1973. Varying doses of uranyl nitrate were given to rats to induce acute renal failure. Increasing doses of uranyl ion produced increased tubular necrosis although blood urea nitrogen (BUN) did not change much between low toxic doses and high toxic doses of uranyl. Saline loading (in drinking water), which suppresses the renin-angiotensin system, ameliorated the increase in BUN but did not protect from tubular necrosis. The authors suggest that passive backflow of glomerular filtrate through necrotic tubules is not responsible for increased BUN, but the renin-angiotensin system may be involved in the renal failure mechanism.

### **11] Studies of Toxic Effects of Uranium in Drinking Water**

Chronic ingestion of uranium in drinking water: a study of kidney bioeffects in humans. M.L. Zamora, B.L. Tracy, J.M. Zielinski, D.P. Meyerhof, and M.A. Moss, *Toxicological Sciences* **43**, 68-77, 1998. This Canadian study compared low-exposure (<1 :g U/L) to high-exposure (2-781 :g U/L) levels in drinking water and found urinary glucose was signif. elevated in the high U intake group. Alkaline phosphatase and  $\exists$ -microglobulin correlated with U intake. Indicators for glomerular injury were not altered in the two groups, indicating the renal tubules are the primary site for renal uranium toxicity.

Inorganic components of drinking water and microalbuminuria. Y. Mao, M. Desmeules, D. Schaubel, D. Berube, R. Dyck, D. Brule, B. Thomas, *Environmental Research* **71**, 135-140, 1995. This study (in Canada) showed an association between cumulative U exposure and albumin (relative to creatinine) in urine. No significant relationship existed for Si, although a trend was observed. It was pointed out that increasing levels of microalbuminuria was observed at U concentration levels below the Canadian Maximum Allowable Concentration (100 microg/L).

Renal effects of uranium in drinking water. P. Kurttio, A. Auvinen, L. Salonen, H. Saha, J. Pekkanen, I. Mäkeläinen, S.B. Väisänen, I.M. Penttilä, and H. Komulainen, *Environmental Health Perspectives* **110**, 337-342, 2002. This Finnish study showed U in drilled wells in this study had a median of 28 :g/L (max. 1920 :g/L). Median daily intake was 39 :g (7-224 :g/d). Found U excretion in urine associated with increased Ca and P excretion. U conc. in drinking water and daily U intake were associated with Ca fractional excretion, but not with P or glucose excretion. Results indicate U affects renal proximal tubules and not glomerulus. Authors indicate safe conc of U in drinking water may be within range of proposed (Finnish) guidelines of 2-30 :g/L.

Uranium daily intake and urinary excretion: a preliminary study in Italy. M Galletti, L D'Annibale, V Pinto, C Cremisini, *Health Physics* **85(2)**, 228-235, 2003. The amount of uranium in drinking water varied from 0.04 to 5.86 microg/L in 29 samples of tap and bottled mineral water. It was estimated that daily dietary intake would be 2.9 to 4.8 microg/day. Found 24 male and 14 females who were not occupationally exposed, 20 to 50 yrs old and living or working in the Rome area had a mean urinary excretion of  $10\sqrt{7}$  nanog/L. Dietary intake from food was also estimated. These data agree with other studies of unexposed individuals in terms of normal urinary U excretion.

Uranium and thorium in urine of united States residents: reference range concentrations. BG Ting, et

al. (8 authors), *Environmental Research, Sec A* **81**, 45-51, 1999). U and Th were measured in the urine of 500 US residents to establish reference range concentrations using ICP-MS. U was detectable in 96.6% of the urine specimens and the 95<sup>th</sup> percentile concentration for U was 34.5 ng/L (i.e., 95% of the urine samples had less than 34.5 ng/L) and the mean concentration was 11.0 ng/L.

Natural uranium concentrations in soft tissues and bone of New York City residents. Fisenne, I.M. and Welford, G.A. *Health Physics* **50**, 739-746, 1986. Found an age dependency for U in lung (including associated lymph) and vertebrae from autopsy specimens of New York City residents, but bone concentrations were a factor of 8 or 9 less than found in other studies. Mean U organ burdens were: 0.5 microg in lung, 0.36 microg in liver, 0.13 microg in kidney, and 6.6 microg in skeleton as measured by a fluorimetric technique on ashed tissue; compared to ICRP Reference Man values of 1.0, 0.45, 7.0 and 59 microg in each organ, respectively. The authors discuss this large discrepancy and recommend reevaluation of the ICRP value.

Occurance of uranium in drinking water in the U.S. Cothorn, C.R. and Lapenbusch, W.L. *Health Physics* **45**, 89-99, 1983. This report from the USEPA gives levels of U in several selected drinking water sources in the US, reported in pCi/L (picoCuries per liter). Of the 59,812 community water supplies in the US, it is estimated that 25 to 650 exceed 20 pCi/L, while 2500 to 5000 exceed 5 pCi/L. They cite a Canadian report that no drinking water in Canadian cities exceeded 4 pCi/L (6 microg/L).

Health effects guidance for uranium in drinking water. Cothorn, C.R., Lapenbusch, W.L. and Cotruvo, J.A. *Health Physics* **44 (Suppl)**, 377-384, 1983. This paper recommends the USEPA adopt a level of 10 pCi/L for uranium in drinking water. The 1976 regulations for radioactivity in drinking water specifically excluded uranium because of uncertainties in its toxicity and occurrence.

Daily U intake in Utah residents from food and drinking water. Singh, N.P., Burleigh, D.P., Ruth, H.M., and Wrenn, M.E. *Health Physics* **59**, 333-337, 1990. This study followed the U intake and excretion of 12 Utah residents and found the average higher than in New York City, San Francisco and Chicago. Average daily excretion of U for these 12 subjects ranged from 2 microg to nearly 10 microg. Average U in drinking water from 12 Salt Lake City locations was 1.46 microg/L. The authors estimate that the ave daily intake of U for the Utah population is about 2 microg.

Maximum permissible amounts of natural uranium in the body, air and drinking water based on human experimental data. Bernard, S.R. *Health Physics* **1**, 288-305, 1958. Eight terminally ill brain tumor patients (age 26 to 63) were injected with uranium compounds (uranyl or uranium tetrachloride) - six were comatose prior to injection. The amount injected (i.v.) ranged from 4 to 50 mg U. Uranyl was cleared rapidly in the urine (69 percent in first day). Autopsies revealed uranyl ion migrates mainly to kidney and bones, whereas U(IV) goes mainly to liver and bones, with similar U burdens in kidneys and bones. This study was intended for the purpose of producing useful data on humans with regard to maximum permissible concentrations. The author states that the kidneys become the critical organ for toxic effects of uranium that limits exposure, rather than the radiation damage, although it is not clear how this conclusion was drawn. This paper was from the Oak Ridge National Laboratory.

Absorption and retention of uranium from drinking water by rats and rabbits. Tracy, B.L., Quinn, J.M., Lahey, J., Gilman, A.P., Mancuso, K., Yagminas, A.P. and Villeneuve, D.C. *Health Physics* **62**, 65-73, 1992. Uranyl nitrate administered in drinking water at levels ranging from 0.46 to 284 mg U/L resulted in about 0.06% of ingested U absorbed from the GI tract. Distribution and retention of U in kidney and bones was similar to that reported for humans, although retention half-time in rabbit bone was much longer than for humans.

## 12] Uranium Aerosols - Inhalation and Mobilization

The International Commission on Radiological Protection (ICRP) classifies clearance of radioactive materials from the human lung following inhalation exposure as: class D - retained for days; class W - retained for weeks; and class Y - retained for years.

Modeling of the dispersion of depleted uranium aerosol. C Mitsakou, K Eleftheriadis, C Housiadas, M Lazaridis, *Health Physics*, **84(4)**, 538-544, 2003. This paper uses mathematical equations based on standard physical properties of matter (e.g., Stokes law) to estimate the distribution of fine particulates that would be found in aerosols from burning depleted uranium. Naturally the distribution will be heavily dependent on wind velocity and other atmospheric conditions, but they calculated that most of the aerosol would settle within a few meters of the release site, although significant amounts will travel more than 1 km even with no wind.

The effect of solubility on inhaled uranium compound clearance: a review. AF Eidson, *Health Physics*, **67(1)**, 1-14, 1994. This is a comprehensive review of rates of clearance of different uranium aerosols, ranging from the insoluble  $\text{UO}_2$ , to relatively soluble  $\text{UO}_3$ , and highly soluble uranyl salts, as well as the uranyl fluorides ( $\text{UF}_6$  and  $\text{UF}_4$ ). It includes studies of lab animals exposed to various uranium compounds, as well as industrial workers. The author categorizes uranium compounds as either rapid, intermediate or slow with regard to their dissolution rates. Although  $\text{UO}_2$  and  $\text{U}_3\text{O}_8$  are classified as slow (half-times of 100 to 10,000 days), the measured half-time for  $\text{UO}_2$  (the least soluble U compound) in several studies was on the order of a year, i.e, hundreds of days rather than thousands of days). Model studies that get long half-times often ignore the complexity of living tissues, e.g., immune systems.

Comparison of early lung clearance of yellowcake aerosols in rats with *in vitro* dissolution and IR analysis. Damon, E.G., Eidson, A.F., Hahn, F.F., Griffith, W.C. and Guilmette, R.A. *Health Physics* **46**, 859-866, 1984. Rats inhaled aerosols of commercial yellowcake powders from different sources and with different properties, including *in vitro* solubilities. These two yellowcake samples contained ammonium diuranate and  $\text{U}_3\text{O}_8$  in very different proportions (82:18 and 25:75), the former with dissolution half time of <1 day and the latter with dissolution half time of >300 days. Initial lung burdens were low (0.014 mg U/kg for one sample and 0.12 mg U/kg for the other). Data indicate a larger percent retention for the low dose sample, although this also contains the more soluble material. Yellowcake aerosol exposures resulted in similar histological changes in kidneys and similar concentrations of U in other tissues as seen with purified uranium compounds.

Techniques for yellowcake dissolution studies *in vitro* and their use in bioassay interpretation. Eidson, A.F. and Griffith, W.C. *Health Physics* **46**, 151-163, 1984. A study of *in vitro* dissolution of yellowcake from different mills and under different solvent conditions, such as salts composition, pH and temperature.

*In vitro* solubility of yellowcake samples from four uranium mills and the implications for bioassay interpretation. Eidson, A.F. and Mewhinney, J.A. *Health Physics* **39**, 893-902, 1980. Solubility in two different solvents (0.1 M HCl and simulated blood serum with DTPA) of yellowcake from four different mills showed variation between 26 and 86% in more soluble form of  $\text{U}_3\text{O}_8$ .

Dissolution fractions and half-times of single source yellowcake in simulated lung fluids. Dennis,

N.A., Blauer, H.M. and Kent, J.E. *Health Physics* **42**, 469-477, 1982. Yellowcake from several different millings were studied for dissolution in simulated lung fluid. Such studies do not reflect lung clearance because they ignore immune response in the lungs.

Inhalation studies of uranium trioxide. Morrow, P.E., Gibb, F.R. and Beiter, H.D. *Health Physics* **23** 273-280, 1972. This study substantiates an earlier study regarding clearance of  $\text{UO}_3$  (uranium trioxide) from lungs following inhalation. The  $\text{UO}_3$  showed a half-time in the lungs of about 4.7 days. U-235 was used to allow radiation measurements to locate uranium burdens in the body. Appreciable amounts of U-235 were found in extrapulmonary structures of the thorax, most likely thoracic lymph tissue through alveolar macrophage clearance.

The clearance of  $\text{UO}_2$  dust from the lungs following single and multiple inhalation exposures. Morrow, P.E., Gibb, F.R. and Leach, L.J. *Health Physics* **12**, 1217-1223, 1966. Showed that single inhalation exposure to  $\text{UO}_2$  aerosols resulted in a 180 day clearance half-time, whereas multiple exposures to aerosols nearly doubled the biological half-time.

Inhalation and intravenous studies of  $\text{UF}_6/\text{UO}_2\text{F}_2$  in dogs. Morrow, P., Gelein, R. Beiter, H. Scott, J., Picano, J. and Yuile, C. *Health Physics* **43**, 859-873, 1982. The intent was to determine effects of exposure to uranyl fluoride ( $\text{UO}_2\text{F}_2$ ) in the absence or presence of HF, a hydrolysis product of  $\text{UF}_6$  that is also toxic. Uranyl fluoride has a very short retention time in the lungs (half-time < 20 min). An absorbed dose of 10 microgrogs uranyl/kg body wt produces renal injury.

Inhaled soluble aerosols insolubilised by lysosomes of alveolar cells. Application to some toxic compounds: electron microprobe and ion microprobe studies. JP Berry, M Meignan, F Escaig, P Galle, *Toxicology*, **52**, 127-139, 1988. Used uranyl nitrate (and other toxic metal ions) in water solution (1%) to make aerosols inhaled by rats for 5 hr/day over 5 days, then used special imaging techniques to measure uranium in lung tissue and alveolar macrophages. Showed that uranium is deposited in lysosomes as insoluble phosphate crystals, similar to what is seen in kidney cells.

Metabolism of uranium in the rat after inhalation of two industrial forms of ore concentrate: the implications for occupational exposure. GN Stradling, JW Stather, SA Gray, JC Moody, M Ellender, A Hodgson, D Sedgwick, N Cooke, *Human Toxicology* **6**, 385-393, 1987. Exposed rats to aerosols of ammonium diuranate and triuranium octoxide ( $\text{U}_3\text{O}_8$ ), major components of yellowcake. The ammonium uranate was cleared from lungs rapidly, mainly to the blood, whereas  $\text{U}_3\text{O}_8$  was removed from lungs by mechanical processes. The body distribution and urinary uranium excretion was much greater for ammonium diuranate. The lung deposit for  $\text{U}_3\text{O}_8$  was 84 percent after 1 day and decreased to 12 percent after 360 days.

The metabolism of ceramic and non-ceramic forms of uranium dioxide after deposition in the rat lung. GN Stradling, JW Stather, SA Gray, JC Moody, A Hodgson, D Sedgwick, N Cooke, *Human Toxicology* **7**, 133-139, 1988. Exposed rats to ceramic or nonceramic uranium dioxide by inhalation or by injecting aqueous suspensions directly into the lungs. Nonceramic uranium dioxide was mobilized from the lung at a slightly faster rate than ceramic form, although the differences were not large. More than 50% of the dose from either form and by either means of administration was removed from the lungs by 84 days. Only about 20% remained in lungs 315 days after inhalation.

Cooper, J.R., Stradling, G.N., Smith, H. and Ham, S.E. The behaviour of uranium-233 oxide and uranyl-233 nitrate in rats. *International Journal of Radiation Biology* **41**, 421-433, 1982. Found that uranium dioxide (<4 nm particle size) and uranyl nitrate in aqueous suspensions given to rats by

pulmonary intubation were transferred to blood at similar rates. It is suggested that the small  $\text{UO}_2$  particles are rapidly oxidized by air and the resulting  $\text{UO}_3$  hydrolyzed to uranyl ion rapidly. Both forms of U react with pulmonary surfactant in vitro, although this binding may not be as important in vivo. It was found that about half the U is bound to protein in blood and the other half about equally divided between the citrate and bicarbonate complexes. The plasma protein binding uranyl ion was identified as transferrin when using human plasma (either albumin or transferrin, or both in rat plasma). U is excreted in urine primarily as the citrate complex.

Metabolism of some industrial uranium tetrafluorides after deposition in the rat lung. Stradling, G.N., Stather, J.W., Strong, J.C., Sumner, S.A., Towndrow, C.G., Moody, J.C., Lennox, A., Dedgwick, D. and Cooke, N. *Human Toxicology* **4**, 159-168, 1985. Two commercially different forms of uranium tetrafluoride were administered to rats by inhalation or by intubation into the lung and were cleared at similar rates from lungs, primarily to the blood, similar to uranyl bicarbonate. This study found much greater transport from lungs than previous studies with other  $\text{UF}_4$  preparations, suggesting this material as ICRP class W.

Relation of particle size of uranium dioxide dust to toxicity following inhalation by animals: II. H.B. Wilson, G.E. Sylvester, S. Laskin, C.W. LaBelle, J.K. Scott, H.E. Stokinger, A.M.A. *Archives of Industrial Hygiene and Occupational Medicine* **6(2)**, 93-104, 1952. Compared uranium dioxide with mean particle diameter of 0.5 micron vs 2.3 micron (both with large range in particle diameters). Found that aqueous suspensions are oxidized in air over a few days (1-2%). Exposure of rats and rabbits to  $\text{UO}_2$  dust of these two particle sizes resulted in greater toxicity with smaller particle size as measured by urinary protein and amino acid nitrogen excretion, as well as greater lung, kidney and bone uranium deposition.

Lobar deposition and retention of inhaled insoluble particulates. H.E. Stokinger, L.T. Steadman, H.B. Wilson, G.E. Sylvester, S. Dziuba, C.W. LaBelle, A.M.A. *Archives of Industrial Hygiene and Occupational Medicine* **4(4)**, 346-353, 1951. Used  $\text{UO}_2$  (ca. 0.45 micron diam.) and  $\text{U}_3\text{O}_8$  (ca 2.6 micron diam.) for dust inhalation exposure of 1 day (6 hr) or 9 days (54 hr) in rats. Found that superior right lobe of lungs had greater deposition rate than other 3 lobes and this lobe also had faster rate of elimination by 10 days. There was 10 times greater deposition of uranium with the smaller particle size dust than with the larger particle size dust.

Relation of particle size of  $\text{U}_3\text{O}_8$  dust to toxicity following inhalation by animals. H.B. Wilson, G.E. Sylvester, S. Laskin, C.W. LaBelle, J.K. Scott, H.E. Stokinger, A.M.A. *Archives of Industrial Health* **11**, 11-16, 1955. Exposed rat and rabbits to 0.5 micron and 2.3 micron particle diameter of  $\text{U}_3\text{O}_8$  dust for inhalation 6 hr/day, 5 days/week for 26 days exposure. Showed greater toxicity with smaller particle size as measured by several parameters of uranium toxicity, including kidney and lung damage.

The solubility of some uranium compounds in simulated lung fluid. N. Cooke, F.B. Holt, *Health Physics* **27**, 69-77, 1974. Looked at solubilities in simulated lung fluid of several uranium compounds used in the nuclear industry with varying particle sizes. This paper and similar papers seem to form the basis for the belief that  $\text{UO}_2$  is not soluble (<3% over 40 days). However, such studies ignore the role of lung macrophages that are known to engulf these particles and bombard them with an array of oxidants that would most likely alter the overall solubility.

The effect of chemical form on the clearance of 239-plutonium from the respiratory system of the rat. J.W. Stather, S. Howden, *Health Physics* **28**, 29-39, 1975. This study looked at plutonium nitrate,

citrate, oxalate, dioxide and DTPA complex, administered by intubation into nasopharyngeal, tracheo-bronchial or pulmonary regions with less than 3 microL injections of 2-3 nCi/kg. The fastest rate of absorption was in the pulmonary region with Pu citrate and nitrate having the greatest absorption rates. Only about 4% of the mobilized Pu (entering the blood) was excreted in the urine, and 2-3 times that amount excreted in feces, and a large percent distributed in body tissue, unlike the clearance of uranium, where most is cleared in urine within a few days.

The clearance of uranium after deposition of the nitrate and bicarbonate in different regions of the rat lung. Ellender, M. *Human Toxicology* **6**, 479-482, 1987. Uranyl solutions administered by direct intubation of solutions into 3 different regions of the lungs (nasopharyngeal, tracheobronchial, and pulmonary) and >90% was cleared from all sites within 24 hr, with pulmonary region giving greatest transfer to the blood. There was little difference between bicarbonate and nitrate salts.

Ghadially, F.N., Yang-Steppuhn, S. and Lalonde, J.-M.A. The effect of uranyl acetate on human lymphoblastoid cells (RPMI 6410) and HeLa cells. *British Journal of Experimental Pathology* **63**, 227-234, 1982. Found that lymphoblastoid cells, but not HeLa cells in culture concentrated uranium in lysosomal compartments (referred to as uraniosomes). The U containing crystals contained uranium, potassium and phosphorus, with traces of sulfur in some but not all deposits. Traces of calcium were found in all extracellular U deposits and some uraniosome deposits.

Deposition pattern and toxicity of subcutaneously implanted uranium dioxide in rats. de Rey, B.M., Lanfranchi, H.E. and Cabrini, R.L. *Health Physics* **46**, 688-692, 1984. Showed that UO<sub>2</sub> deposited under the skin of rats is rapidly mobilized. It appears the particles are engulfed by macrophages and dissolved. Animals died within 6 days following implant doses of 10 mg/kg or more.

### **13] Studies of Uranium Miners**

Radioactivity and lung cancer: a critical review of lung cancer in the miners of Schneeberg and Joachimsthal. Egon Lorenz, *J. Nat. Cancer Inst.* **5**, 1-15, 1944. Concludes that radon cannot be the sole cause of lung cancer in miners, but may also include pneumoconiosis produced from dust in the mines, chronic irritation caused by respiratory diseases, arsenic, radioactive substances and perhaps hereditary susceptibility.

Radiation as the cause of lung cancer among uranium miners. Joseph K Wagoner, Victor E. Archer, Frank E. Lundin, Duncan A. Holaday, and J. William Lloyd, *New Engl. J. Med.* **273**, 181-188, 1965. Studied 3415 underground, white U miners compared with general white male population of the Colorado Plateau. Excess mortality attributed to respiratory neoplasms (22 obs. v 5.7 expected). Conclude that airborne radiation causes respiratory cancers. From dose-response relationship, even when other factors, e.g., cigarette smoking are taken into consideration. Conclude that pathology of U miners was unlike age-smoking-resident matched control group, but was similar to that observed in factory workers exposed to "radiomimetic" agent, mustard gas.

Cancer mortality patterns among U.S. uranium miners and millers, 1950 through 1962. J.K. Wagoner, V.E. Archer, B.E. Carroll, D.A. Holaday, P.A. Lawrence, *J. Nat. Cancer Inst.*, **32**, 787-801, 1964. Report cancer mortality patterns for a group of US uranium miners and millers, with comparison of age-race-cause specific mortality with that of the general male population of the Colorado Plateau. Among white millers, there was no difference in cause-specific mortality relative to general population. Among white U miners with 5 or more years experience, there were 218 deaths compared with 148.7 expected, with respiratory neoplasms about 10 fold higher (11 vs 1.1 expected). The excess

neoplasms was not attributable to age, smoking, nativity, heredity, urbanization, self-selection, diagnostic accuracy and prior hard-rock mining or other ore constituents including silica dust. The evidence implicates airborne radiation in the genesis of this increase in resp. cancer among US U miners.

Uranium ores and depleted uranium in the environment, with a reference to uranium in the biosphere from the Erzgebirge/Sachsen, Germany. A. Meinrath, P. Schneider, G. Meinrath, *J. Environ. Radioact.* **64**, 175-193, 2003. An assessment of the environmental effects of U mining in former East German mines of Erzgebirge under joint Soviet-East German enterprise (WISMUT)

German uranium miner study - historical background and available histopathological material. Horst Wesch, Thorsten Wiethage, Andreas Spiethoff, Kurt Wegener, Klaus-Michael Müller, and Johannes Mehlhorn, *Radiation Research* **152**, S48-S51, 1999. Gives historical bkgd on the Erzgebirge area of Saxony in Germany where many metal ores were mined. About 400,000 workers produced a total of 220,000 tons U during 1946-1990. Documents contain protocols for 28,975 autopsy cases and about 400,000 slides collected from 1957-92, about 66,000 tissue blocks, and 238 whole lungs. From autopsy cases, about 17,466 could be identified as workers of uranium mining. Shows significantly higher incidence of lung cancer in miners rel to area residents. No significant difference for other solid cancers and leukemias.

Radon exposure and lung cancer risk: Czech cohort study. Ladislav Tomášek and Václav Plašek, *Radiation Res* **152**, S59-S63, 1999. Analyzed 2 main factors for radiogenic risk, time since exposure and age at exposure. Find that increasing age at initial exposure to radiation in mines results in less lung disease (lower risk).

Unexpected rates of chromosomal instabilities and alterations of hormone levels in Namibian uranium miners. Reinhard Zaire, Michael Notter, Werner Riedel, and Eckhard Thiel, *Radiation Res* **147**, 579-584, 1997. Shows a much higher prevalence of cancer among **open pit** U miners in Namibia rel to general population. Measured U excretion in urine, neutrophil counts and serum levels of FSH, LH and testosterone, and chromosomal aberrations in whole blood cells. Compared 75 non-smoking, HIV-negative miners with 31 individuals with no occupational mining history. There was 6 fold increase in U excretion among miners, with reduction in testosterone levels and neutrophil count. Also a 3 fold increase in chromosomal aberrations in miners rel to controls. Cells with multiple aberrations among miners, i.e., rogue cells, found for the first time among U miners. Previously only found among acute radiation dose victims in Hiroshima and Chernobyl.

Effects of continuous inhalation exposure of rats to radon and its progeny at various levels of dose and dose rate: Interim results. C.G. Collier, J.C. Strong, S.T. Baker, T. Eldred, J.A.H. Humphreys and L.M. Cobb, *Radiation Res* **152**, S141-S144, 1999. Shows that exposure to radon and radon progeny causes elevated incidences of both benign and malignant lung tumors. The study was not yet complete at time of publication.

Population study in the high natural background radiation area in Kerala, India. M.K. Nair, K.S.V. Nambi, N.S. Amma, P. Gangadharan, P. Jayalekshmi, S. Jayadevan, V. Cherian, and K.N. Reghuram, *Radiation Res.* **152**, S145-S148, 1999. High radiation level due mostly to Th. Of total 400,000 population, 100,000 lived in high radiation areas. Preliminary analysis shows no significant increase in cancer for high exposure group.

Relationships between nasopharyngeal carcinoma and radioactive elements in soils in China. B.

Bølviken, *Medical Hypotheses* **55**, 513-516, 2000. Indicates that title carcinomas are associated with high content of uranium and thorium in soils in China, but cannot rule out inhalation of radon gas or other exposures as contributing factors.

The history of uranium mining and the Navajo people. Doug Brugge and Rob Goble, *Amer. J. Public Health* **92**, 1410-1419, 2002. Gives a good review of health risks from uranium mining and describes health effects of U mining on Navajo people.

Navajo birth outcomes in the Shiprock uranium mining area. L.M. Shields, W.H. Wiese, B.J. Skipper, B. Charley and L. Benally, *Health Physics* **63**, 542-551, 1992. Statistically significant association between U operations and unfavorable birth outcome was identified with the mother living near tailing or mine dumps. Indicates birth defects increased significantly when either parent worked in Shiprock electronics assembly plant. Authors indicate weak association between birth outcomes and radiation exposure. No discussion of possible chemical toxicity from living near mine tailings or mine dumps.

Relationships between nasopharyngeal carcinoma and radioactive elements in soils in China. B. Bølviken, *Molecular Hypotheses* **55**, 513-516, 2000. Epidemiological and geochemical maps of China indicate association between high mortality from nasopharyngeal carcinoma (NPC) and low Mg in soil, but high levels of U and Th are also present in regions with high NPC. The author suggests radioactivity from radon and daughter nuclides may be a contributing factor, but neglects the possibility that U or Th chemical toxicity may play a role.

#### **14] Epidemiology of Uranium Workers and Local Populations**

There have been numerous epidemiological studies of uranium workers and each study will not be reviewed, but are listed here for those interested in finding these studies. To give a gross general summarization, many studies have found a healthy worker effect, *i.e.* workers in the industry were generally healthier than the general population upon hiring and frequently show fewer signs of ill health than their counterparts outside the uranium industry. Several studies show some increases in respiratory problems among uranium workers, including higher incidences of lung cancer in some studies. One must keep in mind that most workers in the uranium industries were closely monitored for exposure and there were strict regulations regarding excessive exposures in many areas of the industry.

Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. MJ Gardner, MP Snee, AJ Hall, CA Powell, S Downes, JD Terell, *British Medical Journal* **300**, 423-429, 1990. Relative risks for leukaemia and non-Hodgkin's lymphoma were higher in children born near Sellafield and in children of fathers employed at the plant, particularly those with high radiation dose recordings before their child's conception.

Mortality among workers at a uranium processing facility, the Linde Air Products Company ceramics plant, 1943-1949. E.A. Dupree, D.L. Cragle, R.W. McLain, D.J. Crawford-Brown, and M.J. Teta, *Scandinavian J. of Work and Environmental Health* **13**, 100-107, 1987. A mortality study of 995 white males employed at this U processing facility in western New York State compared with the white male population of the U.S. and also compared separately with white males in Erie and Niagara counties of New York State shows statistically increased standardized mortality ratios (SMR) for all causes (118), laryngeal cancer (447), all circulatory diseases (118), arteriosclerotic heart disease (119), all respiratory diseases (152) and pneumonia (217) [note, 100 would be the SMR if there is no difference in mortality between exposed workers and controls]. There was also a statistically signif

increase in number of death above expected for laryngeal cancer (5) and pneumonia (17). [Note: although all investigators were affiliated with U.S. institutions, this work was published in a Scandanavian journal].

A mortality study of employees of the nuclear industry in Oak Ridge, Tennessee. EL Frome, DL Cragle, JP Watkins, S Wing, CM Shy, WG Tankersley, CM West, *Radiation Research* **148**, 64-80, 1997. This study showed a strong healthy worker effect, although there were higher death rates at 2 of the 4 facilities relative to the general population, due primarily to non-cancer causes.

Mortality of workers at a nuclear materials production plant at Oak Ridge, Tennessee, 1947-1990. DP Loomis, SH Wolf, *American Journal of Industrial Medicine* **29**, 131-141, 1996. This study reports low overall mortality relative to the general population, although a 20% increase in lung cancers for white males, as well as elevated levels of several other cancers among white males. It also reports increased breast cancer among females, in contrast to a decreased number reported by Frome et al. (1997) above. Such discrepancies need to be closely analyzed.

Uranium dust exposure and lung cancer risk in four uranium processing operations. EA Dupree, JP Watkins, JN Ingle, PW Wallace, CM West, WG Tankersley, *Epidemiology* **6**, 370-375, 1995. This study looked at workers at U processing facilities in Oak Ridge, Tennessee, Mallinckrodt Uranium Division in Missouri and Feed Materials Production Center in Fernald, Ohio. The study identified 787 lung cancer deaths and matched one control to each case. It is left to epidemiologists to examine the methods of this study.

Radiation doses and cause-specific mortality among workers at a nuclear materials fabrication plant. H Checkoway, N Pearce, DJ Crawford-Brown, DL Cragle, *American Journal of Epidemiology* **127**, 255-266, 1988. This is a report of worker mortality at the Y-12 plant in Oak Ridge, Tennessee, with production emphasis on weapons fabrication. It showed a healthy worker effect for most causes, but excess in lung, brain and CNS cancers.

The effects of internal radiation exposure on cancer mortality in nuclear workers at Rocketdyne /Atomics International. B Ritz, H Morgenstern, D Crawford-Brown, B Young, *Environmental Health Perspectives* **108**, 743-751, 2000. Workers at this California facility were monitored for internal radiation exposures during their employment through urinalysis, whole body radiation counts and lung radiation counts. It showed a dose-response relation for death from hematopoietic, lymphopoietic and upper aerodigestive tract cancers. No associations were found for other cancers, including lung cancer. Cancer mortality among workers exposed to chemicals during uranium processing. B Ritz, *JOEM (Journal of Occupational and Environmental Medicine)* **41(7)**, 556-566, 1999. This study found increased mortality from liver cancer among workers exposed to trichloroethylene, laryngeal and other cancers among workers exposed to cutting fluid. Kerosene exposure increased death rates for digestive-tract cancers and prostate cancer. Exposures were assessed historically by plant experts for plant areas and job titles. Internal radiation exposure from uranium were assessed by urinalysis data but it isn't clear whether radiation exposure was factored into this analysis.

A comparison of uranium cases showing long chest burden retention. West, C.M. and Scott, L.M. *Health Physics* **12**, 1545-1555, 1966. Internal exposure to uranium for about 2500 personnel at the Y-12 Oak Ridge facility were evaluated. Normal elimination of U chest burdens, measured by gamma spectrum measurements of the chest, were observed for all but 5 cases. U excretion in these 5 decreased more rapidly than the chest burden. The biological half-lives for chest burden in these 5 was between 380 and 1470 days. No explanation is offered for these long retention times, but it would

seem they are due to migration of the U load to thoracic lymph as a result of alveolar macrophages. Why these 5 and not the others? Perhaps it is due to the nature of the uranium compounds that entered the lung. Perhaps it is due to their genetic make-up and/or physiological differences. See next entry.

Uranium cases showing long chest burden retention - an update. West, C.M. and Scott, L.M. *Health Physics* **17**, 781-791, 1969. Data on 4 of the 5 above workers over an additional 3.5 yrs since the above report shows a urine to fecal U elimination ratio of about 1, indicating an unusually high fecal clearance. No explanation is given for this unusual pattern of excretion, although one explanation might be that the lymphatic stores of U removed from the lungs may be getting into the bile for elimination in the feces.

### **15] Papers from the Baltimore VA Study of DU Exposed 1991 Gulf War Veterans**

Detection of depleted uranium in urine of veterans from the 1991 Gulf War. RH Gwiazda, K Squibb, M McDiarmid and D Smith, *Health Physics* **86(1)**, 12-18, 2004. This paper describes the ICP-MS analysis of urine from Gulf War vets with retained shrapnel. It is significant that a polyatomic substance with mass 234.81 is resolved at a resolution of 4000 m/deltam, whereas at a resolution of 300 m/deltam it appeared that the uranium in urine was enriched uranium because of the contribution of the polyatomic substance interfering with the U-235 peak (235.04). This shows that an instrument with high resolution must be used to give reliable results regarding measurements of depleted uranium in urine, i.e., to give correct isotope ratios.

Determination of the isotopic composition of uranium in urine by inductively coupled plasma mass spectrometry. JW Ejnik, AJ Carmichael, MM Hamilton, M McDiarmid, K squibb, P Boyd and W Tardiff, *Health Physics* **78(2)**, 143-146, 2000. This study used dry ashing of urine at 450 C followed by wet ashing with additions of concentrated nitric acid and 30% hydrogen peroxide. The ash was dissolved in 1 M nitric acid prior to ICP-MS analysis. When urine U was greater than 150 ng/L, the percent U-235 in DU exposed individuals was between 0.20 and 0.33% (as expected). Those unexposed to DU had urine uranium less than 50 ng/L and U-235 percentage consistent with natural uranium (0.7 to 1.0%). The authors claim a minimum concentration of 14 ng/L was needed to identify whether the uranium was depleted or natural, although the high percent U-235 in several samples would indicate the instrument or the method was not reliable for these measurements. See also the above paper (Gwiazda et al) regarding this problem.

Elevated urine uranium excretion by soldiers with retained shrapnel. FJ Hooper, KS Squibb, EL Siegel, K McPhaul and JP Keogh, *Health Physics* **77(5)**, 512-519, 1999. This paper discusses the initial study population. There were 33 participants out of 68 identified to be involved in "friendly fire" incidents, of which 15 had DU shrapnel, although a total of 17 had some kind of shrapnel by x-ray examination. Blood and urine were analyzed by standard clinical tests, although not all data are reported (in particular data that would indicate kidney damage). Veterans with DU shrapnel were excreting elevated levels of U in urine. There are several scientifically questionable practices in this report.

Surveillance of depleted uranium exposed Gulf War veterans: health effects observed in an enlarged "friendly fire" cohort. M. McDiarmid, K. Squibb, S. Engelhardt, M. Oliver, P. Gucer, P.D. Wilson, R. Kane, M. Dabat, B. Kaup, L. Anderson, D. Hoover, L. Brown, D. Jacobson-Kram, *Journal of Occupational and Environmental Medicine (JOEM)* **43**, 991-1000, 2001.

Health effects of depleted uranium in exposed Gulf War veterans. M.A. McDiarmid, J.P. Keogh, F.J. Hooper, K. McPhaul, K. Squibb, R. Kane, R. DiPino, M. Kabat, B. Kaup, L. Anderson, D. Hoover, L.

Brown, M. Hamilton, D. Jacobson-Kram, M. Walsh, *Environmental Research* (Section A) **82**, 168-180, 2000. This paper compares 29 “exposed” veterans, of which 15 had embedded DU shrapnel, with 38 “nonexposed” veterans, many of whom are not healthy, including neurological problems. There are comparisons of the two “groups” with regard to psychiatric and neurocognitive assessments, as well as levels of neuroendocrine hormones. There are indications that high levels of uranium in urine correlate with changes in some of the neurological parameters studied. Handling of data and many practices in this report are of questionable scientific rigor.

Urinary uranium concentrations in an enlarged Gulf war veteran cohort. MA McDiarmid, SM Engelhardt and M Oliver, *Health Physics* **80(3)**, 270-273, 2001. This paper reports urine analysis of 169 Gulf war vets for uranium concentrations. Twelve individuals exhibited elevated uranium, although repeat analysis of 6 out of these 12 resulted in 3 being classified as low uranium excreters. This paper is of questionable scientific value. Data are presented in ways that make it difficult or impossible to compare those exposed to high levels of DU with unexposed individuals in the study.

The utility of spot collection for urinary uranium determinations in depleted uranium exposed Gulf war veterans. MA McDiarmid, FJ Hooper, K Squibb and K McPhaul, *Health Physics* **77(3)**, 261-264, 1999. This study showed that a creatinine standardized spot sample and a 24 hr uncorrected sample were both highly correlated with a creatinine corrected 24 hr collection, although the correlation was not as good when a low uranium subset group was taken. Uncorrected spot samples, unadjusted for volume and creatinine had the lowest correlation.

Increased frequencies of sister chromatid exchange in soldiers deployed to Kuwait. M.A. McDiarmid, D. Jacobson-Kram, K. Koloder, D.P. Deeter, R.M. Lachiver, B.G. Scott, B.P. Petrucelli, D. Gustavison, D. Putman, *Mutagenesis* **10**, 263-265, 1995. Blood was collected from 61 soldiers prior to deployment to Kuwait in 1991 and additional blood samples taken after 2 months in Kuwait and one month after return to Germany. Sister chromatid exchange frequency was significantly elevated ( $P < 0.001$ ) after deployment and persisted for at least 1 month after return to Germany. Outcome was not affected by smoking, age or diet. Factors contributing to increased SCE frequency are discussed, although depleted uranium is not mentioned in this discussion.

## **16] DU and Other Environmental Toxins in Veterans**

Pregnancy outcomes among U.S. Gulf War veterans: a population-based survey of 30,000 veterans. H Kang, C Magee, C Mahan, K Lee, F Murphy, L Jackson, G Matanoski, *Annals of Epidemiology* **11**, 504-511, 2001. A survey was conducted of 15,000 Gulf War veterans in four military branches and 3 unit components (active, reserve and National Guard) and compared with 15,000 non-Gulf veteran controls. Both male (odds ratio, 1.62) and female (OR, 1.35, not statistically significant) Gulf veterans reported a higher rate of miscarriage and birth defects among live births, relative to controls.

Impact of the Gulf war on congenital heart diseases in Kuwait. L Abushaban, A Al-Hay, B Uthaman, A Salama, J Selvan, *International Journal of Cardiology* **93**, 157-162, 2004. A retrospective study of CHD in babies born in Kuwait before the Gulf war and after the Gulf war shows the incidence of CHD (per 10,000 live births) was 39.5 before the war and 103.4 after the war ( $P < 0.001$ ). The greatest increase was in the immediate 3 years after the invasion, with some reduction in the period from 1995 to 2000. It is not known what factors contribute to this observation.

Determination of depleted uranium, pyridostigmine bromide and its metabolite in plasma and urine following combined administration in rats. A.W. Abu-Qare and M.B. Abou-Donia, *Journal of*

*Pharmaceutical and Biochemical Analysis* **26**, 281-289, 2001.

Health effects of the 1991 Kuwait oil fires: a survey of US army troops. B.P. Petrucci, M. Goldenbaum, B. Scott, R. Lachiver, D. Kanjarpane, E. Elliott, M. Francis, M.A. McDiarmid, D. Deeter, *Journal of Occupational and Environmental Medicine* (JOEM) **41**, 433-439, 1999.

Reproductive hazards and firefighters. M.A. McDiarmid and J. Agnew, *Occupational Medicine* **10**, 829-841, 1995.

### **17] Embedded DU Fragments**

The biokinetics of uranium migrating from embedded DU fragments. R.W. Leggett and T.C. Pellmar, *Journal of Environmental Radioactivity* **64**, 205-225, 2003. This paper compares biokinetic data for U distribution and toxicity in rats [published by Pellmar et al., *Toxicol. Science* **49**, 29-39, 1999, below] with other published data of different forms of U. The data indicate that U migrating from embedded DU fragments behaves similar to other forms of U exposure with regard to long term accumulation in kidney, bone and liver. The authors admit there is insufficient data to compare lymph nodes, brain and testes.

Distribution of uranium in rats implanted with depleted uranium pellets. T.C. Pellmar, A.F. Fuciarelli, J.W. Ejniak, M. Hamilton, J. Hogan, S. Strocko, C. Emond, H.M. Mottaz and M.R. Landauer, *Toxicological Sciences* **49**, 29-39, 1999. Found highest concentrations of U in kidney and bone (tibia and skull). There was also significantly increased level of urinary U over the time course of the study for DU implanted animals relative to tantalum implanted controls. Other tissues with significant increases of U deposits in muscle, spleen, liver, heart, lung, brain, lymph nodes and testes.

Implanted depleted uranium fragments cause soft tissue sarcomas in the muscles of rats. F.F. Hahn, R.A. Guilmette and M.D. Hoover, *Environmental Health Perspectives* **110**, 51-59, 2002. Radiographs showed corrosion around DU implants shortly after placement. There was an increase in soft tissue sarcomas in rats with larger (5x5 mm squares) of DU metal and with Thorotrast. Smaller squares of DU (2.5x2.5 mm) and tantalum (5x5 mm squares) had slightly more sarcomas than smallest DU (2x1 mm squares) or surgical controls (no metal implant).

Biological effects of embedded depleted uranium (DU): summary of Armed Forces Radiobiology Research Institute research. DE McClain et al (13 authors), *Science of the Total Environment* **274**, 115-118, 2001. Summarizes studies on rodents at AFRRI.

### **18] General Discussions and Editorials on DU and Gulf War Syndrome**

Toxicity of depleted uranium (Commentary). N.D. Priest, *Lancet* **357**, 244-246, 2001. Discusses the radioactivity of DU and states that 90% of uranyl ion that enters the bloodstream is excreted in urine within 24 hr after intake, with most of the remainder being excreted within the following weeks and only a few percent being retained in the skeleton. He states some U is present in semen, and is not unexpected because body fluids contain  $\text{Ca}^{2+}$  - this is where Priest loses credibility, because he indicates "uranyl ion shares many chemical and biological properties with the alkaline earth ions." (citing ref 3, paper by Priest). He goes on to state the "**uranium is not deposited in either the testis or ovary, and genotoxic effects of uranium have not been describe in either animals or man.**" He also claims "**Although uranium binds strongly to nucleic acids in vitro and is used to stain tissue sections for electron microscopy, no chemical mutagenicity has been demonstrated for this**

**element in mammals. By contrast radiation is mutagenic."** There were at least 2 articles prior to 2000 (see above) reporting genotoxicity or transformation of human cells to tumorigenic phenotypes. He then goes on to argue that DU has low specific radioactivity and therefore could not be causing mutations, genotoxicity and other effects. He argues that only soluble uranium is chemically toxic (reasonable assumption), but that "soluble U is largely absent from the lungs" because inhaled deposits are rapidly transferred to the bloodstream. He argues that American servicemen with DU shrapnel deposits have no evidence of health effects. It seems many of Priest's arguments are unsound, yet this article has been frequently cited to support lack of evidence for DU being a health risk.

Undiagnosed illnesses and radioactive warfare. A. Durakovi , *Croatian Medical Journal* **44(5)**, 520-532, 2003. This paper gives an overview of nuclear weapons proliferation and development of radiological weapons, then discusses the toxicity of uranium in the context of Gulf War I and the Balkan wars. It also includes discussion of studies undertaken by the Uranium Medical Research Center in Afghanistan, indicating high levels of non-depleted uranium (i.e., not depleted in U-235, but also containing U-236, which is indicative of uranium having gone through processing) at many bomb sites in Afghanistan. Clinical data from Afghanistan were not reported in this paper.

On depleted uranium: Gulf War and Balkan Syndrome. A. Durakovi , *Croatian Medical Journal* **42(2)**, 130-134, 2001. This paper calls for the need to take a serious look at whether depleted uranium is contributing to the broad array of illnesses that have come to be known as Gulf War syndrome, considering the toxicity of uranium that is recognized by many international nuclear agencies.

From Gulf War syndrome to Balkan War syndrome. S. Lang, *Croatian Medical Journal* **42**, 205-209, 2001. This discusses the possible connections between depleted uranium munitions and illnesses suffered by soldiers.

Invited editorial: Recent studies of mortality and cancer morbidity experience of uranium workers and a fresh look at depleted uranium. R.L. Kathren, *Journal of Radiological Protection* **21**, 105-107, 2001. Argues that "radiological hazards are trivial", but this ignores the "bystander effect" shown by Nagasawa and Little in 1992 (see above). Protection standards are based on potential chemotoxic effects on the kidney, inferred from animal studies. He states there has never been a study, epidemiological or otherwise, that has demonstrated deleterious kidney effects on humans, even though reports of large U intake indicated increased proteinuria. Indicates apparent excess of morbidity and mortality of Hodgkin's disease and non-Hodgkin's lymphoma in Springfield workers bears additional study and scrutiny.

Depleted uranium and radiation-induced lung cancer and leukaemia (Commentary). R.F. Mould, *The British Journal of Radiology* **74**, 677-683, 2001. Gives background on DU use in Gulf War and suggests that uranyl competes with  $\text{Ca}^{2+}$  for transport mechanisms and ca. 66% of total body burden is in skeleton (see studies in rats and mice indicating high levels in soft tissues). Discusses U industries, radiation, and finally lung cancer and leukaemia in Gulf War vets. Indicates radiation levels are too low for DU to cause these diseases in exposed vets. Some good refs in this article.

After the dust settles. Steve Fetter and Frank von Hippel, *The Bulletin of the Atomic Scientists* **55**, 42-45, 1999. They conclude that radiological effects from DU exposure will be minor, but people exposed to vehicles hit by DU munitions, their rescuers, and individuals who spent prolonged time in the vehicles as part of cleanup details without adequate respiratory protection could be at high risk for heavy-metal toxicity from inhalation of DU dust.

Depleted uranium - is it really a health issue? H.A. Lee, R. Gabriel, P. Bolton, *Lancet Oncology* **2**, 197, 2001. Indicate 3 to 70% of DU munitions aerosolise upon impact with heavily armoured targets. They indicate that most of the DU munitions in the Gulf War 1991 conflict were fired from aircraft, so would have missed their targets! Consequently it would be buried deep in the soil adding slightly to the natural U already present in soil. They indicate that DU munitions striking light armour or soft-skinned vehicles and even buildings with reinforced concrete would not cause the DU to aerosolise. They use the usual references to back up their arguments. This was in response to an article: Mixed messages about DU, *Lancet Oncology* **3**, 65, 2001. (Vol numbers don't seem to agree - it refers to Feb article in vol 3, but this is marked as April issue, vol 2).

Depleted uranium (DU): a holistic consideration of DU related matters. E.I. Hamilton, *The Science of the Total Environment* **281**, 5-21, 2001. The abstract states "unnecessary and costly confusion has existed for some 11 years concerning the hazard it [DU] constitutes, despite the fact that sufficient data are available to answer most of the relevant questions." This article discusses DU in the environment of the UK in the vicinity of the British Nuclear Fuels, Ltd. in Cumbria. However, there are numerous articles cited by Hamilton regarding health and environmental considerations of uranium.

Desert Storm Syndrome: sick soldiers and dead children? Ian Doucet, *Medicine and War* **10**, 183-194, 1994. Describes symptoms of GWS (Gulf War syndrome) as different from post-traumatic stress syndrome as reported after previous conflicts and suggests some resemble a direct effect on the immune system. Discusses possible causes, including post-traumatic stress disorder, infection, prophylactic medicine, exposure to chemical and biological warfare agents, exposures resulting from oil spills and fires, and exposure to depleted uranium. He suggests a multiple assault on the body's immune system.

Depleted uranium: a new battlefield hazard. V.S.G. Murray, M.R. Bailey, B.G. Spratt, *Lancet (Supplement)* **360**, S31-S32. The authors are members of the Royal Society Working Group on the Hazards of Depleted Uranium Munitions. They conclude that the radiation from DU is not sufficient to warrant concern about increases in lung cancer or other cancers such as leukemia. They go on to say that the critical organ for chemical toxicity effects is the renal proximal tubule epithelium, but with severe exposures could cause hepatic, haemological, respiratory and cardiac toxic effects. They mention that data regarding exposures are poor and there are problems with trying to predict long term effects. They suggest the health hazards of long-term DU are minimal compared to the inherent hazards of war.

Does Iraq's depleted uranium pose a health risk? (News story) Karen Birchard, *Lancet* **351**, 657, 1998. Reports that Bill Griffin, an Irish petrochemical engineer, compiled a literature review and sent it to the UN Commissioner for Human Rights hypothesizing that the current health and environmental problems in Iraq may be linked to DU weapons use in the 1991 conflict. The report notes that the death rate per 1000 Iraqi children under 5 yrs rose from 2.3 in 1989 to 16.6 in 1993. Cases of lymphoblastic leukemia more than quadrupled. In men, lung, bladder, bronchus, skin and stomach cancers show the greatest increase. In women, the greatest increases are in breast and bladder cancer, and non-Hodgkin lymphoma. Congenital malformations have also increased, as have diseases of the immune system.

Depleted uranium and public health: fifty years' study of occupational exposure provides little evidence of cancer. (Editorial) Melissa A. McDiarmid, *BMJ (British Medical Journal)* **322**, 123-124, 2001. Reports that USCDC, Agency for Toxic Substances and Disease Registry, concluded that "no significant differences in cancer [of the lungs] was found between workers who are occupationally exposed to uranium and control populations" A review of >11 studies in U miners attributed and

observed increase in lung cancer to radon and its progeny and not to U. Long term animal studies with both natural and enriched U had negative (9) or equivocal (3) results for carcinogenicity. Further evidence comes from surveillance of victims of friendly fire, 15 with retained DU fragments in soft tissue and excreting raised U in urine. None of these vets has leukemia, bone cancer or lung cancer (although mental deficits, which did increase in this group) is not mentioned in this editorial.

WHO sends team to Iraq to investigate effects of depleted uranium. (News story) Clare Kapp, *Lancet* **358**, 737, 2001. An 8 member WHO team travelled to Iraq on Aug 27 to finalize plans for studies into claims of an increase in congenital malformations, cancers and renal disease as a result of DU from 1991 conflict. This investigation was stopped by a vote in the General Assembly, 54 to stop it, 45 to continue and 45 abstentions. The U.S. was reported to have lobbied strongly to have this study stopped and may have intimidated many countries that rely on U.S. aid.

### **19] Civil and Military Uses of DU**

Civil Uses of Depleted Uranium, Maria Betti, *J. Environ. Radioact.* **64**, 113-119, 2003. Describes the nature of DU and uses include: in glassware and ceramics, for jewelry enamel and badges, used in dental porcelains (<1.4%) until 1980s, as a chemical catalyst, for radiation shielding in nuclear industry, as counterbalance for aircraft (McDonnell-Douglas DC-10, Lockheed L-1011, Boeing 747), boats and in the oil and gas exploration industries. The paper also discusses the exposure of airline workers and passengers to radiation from DU in counterweights.

Properties, use and health effects of depleted uranium (DU): a general overview. A. Bleise, P.R. Danesi, W. Burkart, *J. Environ. Radioact.* **64**, 93-112, 2003. Concludes that the risk of health effects from DU would be minimal.

Civilian and military uses of depleted uranium: environmental and health problems. Chiara Cantaluppi and Sandro Degetto, *Annali di Chimica* **90**, 665-676, 2000. Emphasizes risk to kidneys from chemical toxicity of internalized DU. Radiation poses minimal risk even for internal DU.

### **20] Thorotrast (Th232) Toxicity**

Revised organ partition of thorium-232 in Thorotrast patients. Y. Ishikawa, J.A.H. Humphreys, C.G. Collier, N.D. Priest, Y. Kato, T. Mori and R. Machinami, *Radiation Research* **152**, S102-S106, 1999.

Cancer mortality of Thorotrast patients in Japan: the second series updated 1998. C. Kido, F. Sasaki, Y. Hirota, K. Kiyosawa, S. Hayashi, T. Mori and T. Sobue, *Radiation Research* **152**, S81-S83, 1999.

Summary of entire Japanese thorotrast follow-up study: updated 1998. T Mori et al., *Radiation Research* **152**, S84-S87, 1999.

The German thorotrast study: recent results and assessment of risks. G vanKaick et al., *Radiation Research* **152**, S64-S71, 1999.