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Toxicity of uranium

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Toxicity of Uranium:

A Brief Review with Special Reference to Man

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General Historical Aspects of Uranium Toxicity

- ▶ U discovered in 1789 by Martin Klaproth
- ▶ Early toxicity studies in animals by Gmelin (1824) indicated orally ingested U “a feeble poison”
- ▶ Later animal studies (Manhattan Engineering District, WWII) established both chemical toxicity and radiotoxicity – different mechanisms for each
- ▶ Chemical toxicity dominates at low enrichments (for soluble compounds).

Toxic Action Comparison



- ▶ **Radiotoxicity -- stochastic effects (i.e. carcinogenesis); frequency proportional to dose; no threshold; severity unrelated to dose. (Increases with enrichment)**
- ▶ **Chemical toxicity – deterministic effects; threshold with severity/type related to dose. (Independent of enrichment)**

Acute Chemical Toxicity in Animals



Variations in interspecies sensitivity: Based on g of U per kg of body weight, species sensitivity follows this ordering

rabbit > rat > guinea pig > mouse

Rabbit is ~40 times more sensitive than mouse

Extrapolation to Humans: LD₅₀



- ▶ Let's look at rats, a relatively sensitive species; a species for which much data are available.
- ▶ Oral LD₅₀ for uranyl fluoride (soluble and hence more toxic) U in rats is 540 mg/kg per day for 30 days (~254 mg of U/kg of body weight) [Maynard and Hodge 1949]
- ▶ Now let us use a linear extrapolation of g of U/kg of body weight and apply it to man. This corresponds to daily oral intake of 37.8 g of the compound or 29.2 g of U for 70 kg reference man

Extrapolation to Humans: LD₅₀



- ▶ Which corresponds to a peak kidney concentration of 794 mg U or 2.6 mgU/gkidney based on IMBA-URAN calculation (after 30 days of intake)
- ▶ Which in turn equates to an acute inhalation intake of 31.6 g of uranyl fluoride (~ 24.4g of U) assuming an AMAD = 5 micrometers (typical particle size seen in industrial settings).

Establishment of Toxic Level



- ▶ **Systemic: 114 mg (McGuire 1991) as determined by expert panel largely from animal data and opinion**
- ▶ **Corresponds to oral intake of ~ 5.7 g (assumes $f_1 = 0.02$)**
- ▶ **Equates to inhalation intake of 1.0 g based on 5 μm AMAD Type F soluble aerosol (Kathren and Burklin 2008)**



Which species best resembles me?



Extrapolations from animal data have inherently large and unknown uncertainties.

Human Exposure to Uranium



- ▶ There are **no reported or documented deaths** in humans from acute or chronic intake of U
- ▶ Prior to discovery of insulin in 1921-22 by Banting and Best, oral administration of U was used as therapy for diabetes
- ▶ Therapeutic doses of **several grams** administered daily *per os* have been reported in at least 2 dozen patients **without fatalities**.

Diabetes Therapy Doses



Reference	Estimated Oral Intake (g U)	Calculated Peak Kidney Burden from Ingestion (mg U)	Calculated Acute Inhalation Required to Produce Equivalent Kidney Burden (mg U)
Bond (1898) Case 1	268	25	750
Bond (1898) Case 9	1329	120	3800
Duncan (1897) Case 1	40	24	740
Duncan (1897) Case 2	31	33	1000
Duncan (1897) Case 3	94	65	2000
Duncan (1897) Case 4	111	51	1600
Duncan (1897) Case 5	50	32	990
West (1895) Case 1	101	52	1600
West (1895) Case 3	38	39	1200
West (1896) Case 3	27	24	730
Bradbury (1896)	178	38	1200

Diabetes Therapy Doses



- ▶ **Wilcox reported reduced thirst and polyuria, along with glucosuria in 46 of 54 diabetic patients treated over extended periods from months to years with daily doses up to 200 mg of uranyl nitrate.**
- ▶ **“In all instances in which I have employed uranium nitrate I have never noted any untoward gastric or intestinal symptom nor any signs of blood or renal disturbances; careful observation has been especially directed toward early detection of the latter.” (Wilcox 1917)**

Diabetes Therapy Doses



- ▶ **Physicians then did not have the sophisticated tests currently available to assess of infer kidney damage.**
- ▶ **No one in the previous table had reported long term follow up.**
- ▶ **Nonetheless, these data are significant and strongly support that uranium is not of a particularly high order of acute toxicity in man.**

Planned Administrations



- ▶ **University of Rochester (1948) 6 subjects**
- ▶ **Boston IV Injections (1955) 8 subjects**
- ▶ **Butterworth (1955) 1 subject**
- ▶ **Hursh et al. Oral uptake (1969) 4 subjects**
- ▶ **Harris inhalation experiment (1961) 1 subject**

- ▶ **All involved fairly small doses; no fatalities from U**

Cases Involving Injections (Type F or Type M) Uranium



Paper	Calculated Peak Kidney Burden from Injection (mg U)	Calculated Acute Inhalation of Type F Uranium Required to Produce Equivalent Kidney Burden (mg U)
Hursh and Spoor- Boston Injection Experiment Case 6	3.5	110
Hursh and Spoor- Boston Injection Experiment Case 7	2.9	97
Hursh and Spoor- Boston Injection Experiment Case 8	3.2	90

Note: For cases 7 and 8, the actual oral intake was Type M material, but the acute inhalation intake was calculated for Type F material. (This is because IMBA-URAN calculates the same kidney burden for a given activity in the urine regardless of the type of material.)

Case of Deliberate Intake



- ▶ **Attempted suicide** (Pavlakakis et al 1996)
 - ◆ Ingested single dose of ~8.4 g U as acetate
 - Uptake estimated at 168 mg ($f_1 = 0.02$)
 - Treated by chelation (Ca EDTA, Ca DTPA) which failed to increase urinary excretion
 - Rhabdomyolysis, anemia, myocarditis, liver dysfunction, paralytic ileus, acute renal failure and glucosuria
 - Six months after intake suffered from acute renal impairment and incomplete Fanconi's syndrome
 - ◆ He survived, but was heavily treated

And now, the rest of the story ...



- ▶ **Had extensive medical history including personality disorder, gastrointestinal ulcers (may have significantly enhanced uptake), hypertension, hyperlipidemia, asthma, migrane, gout, renal calculi and urinary infections, among others**
- ▶ **Self-medicator and drug abuser – had taken 14 drugs in year preceding his suicide attempt. (The effects of the various drugs on the absorption of uranium is unknown.)**

Accidental Exposures



- ▶ Relatively few cases
- ▶ Mostly involving UF₆
- ▶ Typically, single massive acute exposure
- ▶ HF effects – pulmonary edema
- ▶ Other effects (e.g. burns as in Chinese case) may affect response to U
- ▶ Transitory inferential kidney effects may also be attributable to stress or other causes

No known deaths in humans attributable to U

Threshold for Chemotoxic Effects



- ▶ **Based largely on animal studies, kidney is considered the most sensitive organ**
- ▶ **Generally accepted nephrotoxic threshold level = 3 $\mu\text{g U}$ per g of kidney (\sim 1 mg total) (Brotsky 1996; ATSDR 1999; National Academies (2000); Royal Society (2002 and many others))**
- ▶ **Some think level is too high and should be reduced (Morrow 1982; Leggett 1989; Zhao and Zhao 1990)**

Conclusions



- ▶ **High acute doses in animals can cause death**
- ▶ **Sensitivity varies among species**
- ▶ **There has never been a death attributable to uranium poisoning in humans**
- ▶ **Humans seem to be less sensitive to both acute and chronic chemotoxic effects of uranium than other mammalian species studied**
- ▶ **Insoluble compounds reportedly nontoxic**
- ▶ **Kidney is accepted as primary organ of concern for chemotoxicity and chronic exposure limits**

The Bottom Line



- ▶ **Although the data on which to establish oral and inhalation acute LD₅₀ for uranium in man are sparse, they appear adequate to conclude that the LD₅₀ for oral intake of soluble uranium compounds exceeds several grams of uranium and for inhalation intakes is at least, greater than 1.0 g, and likely significantly greater.**

Recommended Provisional Acute LD₅₀ Doses



- ▶ **For acute oral intake of soluble U: 5 g**
(~70 mg/kg based on Reference Man)
- ▶ **Acute inhalation intake of soluble U: 1 g**
(14 mg/kg based on Reference Man)
- ▶ **Above are most restrictive cases; LD₅₀ for insoluble U compounds is much higher**



Questions?

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