Acute Toxicity of Uranium:
A Brief Review with Special Reference to Man

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General Aspects of Uranium Toxicity

- ✓ U discovered in 1799 by Klaproth
- ✓ Early toxicity studies in animals by Gmelin (1824) indicated ingested U is "a feeble poison"
- ✓ Later studies (Manhattan District, WWII) established both chemical toxicity and radiotoxicity
- ✓ Chemical toxicity dominates at enrichments below about 15% U-235

Acute Toxicity in Animals

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

rabbit > rat > guinea pig > mouse

Rabbit is ~40 times as sensitive as mouse

Humans at lower end of sensitivity scale

Extrapolation to Humans

Using rats, a relatively sensitive species for which much data are available, and linear extrapolation of g of U/kg of body weight:

Oral LD_{50} for uranium nitrate hexahydrate (soluble and hence more toxic) U in rats is 540 mg/kg per day (~254 mg of U/kg of body weight)

This corresponds to daily oral intake of 37.8 g of the compound or 18 g of U for 70 kg reference man

- More recently, Domingo et al.(1987 -- cited in ATSDR Toxicological Profile on U) indicate that the acute oral LD_{50} in rats and mice for a single intake is *at least* 100 mg U per kg of body weight based on uranium acetate

- This equates to 7 g for a 70 kg man, or about 1/3 of what was determined for the hexahydrate

Human Exposure to Uranium

- There are no reported deaths in humans following acute or chronic intake of U due to 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

Cases Involving Large Oral Intakes of Soluble (Type F) Uranium

Paper	Oral Intake (gU)	Calculated Peak Kidney Burden from Ingestion (mgU)	Calculated Acute Inhalation Required to Produce Equivalent Kidney Burden (mgU)
Bond Case 1	268	2.5E+01	7.5E+02
Bond Case 9	1329	1.2E+02	3.8E+03
Duncan Case 1	40	2.4E+01	7.4E+02
Duncan Case 2	31	3.3E+01	1.0E+03
Duncan Case 3	94	6.5E+01	2.0E+03
Duncan Case 4	111	5.1E+01	1.6E+03
Duncan Case 5	50	3.2E+01	9.9E+02
West (1895) Case 1	101	5.2E+01	1.6E+03
West (1895) Case 3	38	3.9E+01	1.2E+03
West (1896) Case 3	27	2.4E+01	7.3E+02
Bradbury	178	3.8E+01	1.2E+03

Involving Injections (Type F or Type M) Uranium

Paper	Calculated Peak Kidney Burden from Injection (mgU)	Calculated Acute Inhalation of Type F Uranium Required to Produce Equivalent Kidney Burden (mgU)
Hursh and Spoor- Boston Injection Experiment Case 6	3.5E+00	1.1+02
Hursh and Spoor- Boston Injection Experiment Case 7	2.9E+00	9.7E+01
Hursh and Spoor- Boston Injection Experiment Case 8	3.2E+01	9.0E+01

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.)

Planned Administrations

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

- All involved small doses; no fatalities

Self-Administered – Attempted Suicide

- Individual attempted suicide by taking the equivalent of 9.1 g soluble U for a 70 kg man.
- Chelation therapy applied
- Many health problems; including significant renal impairment and persistent incomplete Fanconi's syndrome. History of mental illness.
- Unknown if the individual would have survived without treatment.
- Individual had regularly taken 14 drugs, a number of topical agents, including antifugals and steriods in 12 months prior to suicide attempt.
- Unknown what effect these medicines had.

Self-Administered – Attempted Suicide

- History of gastrointestinal ulcerations
- "It is likely that an impaired muscosal barrier aided absorption and significantly increased his toxic insult"
- All effects other than kidney and glycosuria related effects likely due to other causes
- Fanconi's syndrome can be caused by medications
- Limited credence should be placed on this case.

Accidental Exposures

- Relatively few cases
- Mostly involving UF_6
  - Single massive acute exposure
  - HF effects
  - Transitory kidney effects

No deaths attributable to U

Establishment of Toxic Level

- Systemic: 114 mg McGuire (1991)
- Corresponds to oral intake of ~ 5.7 g (assumes $f_1 = 0.02$)
- Equates to inhalation intake of 0.41 g based on 5 µm AMAD Type F soluble aerosol

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 toxic effects of uranium than other mammalian species studied
- Insoluble compounds certainly less harmful from a chemical perspective and have reportedly been reported as nontoxic

The Bottom Line

- Although the data on which to establish oral and inhalation acute LD_{50} for uranium in man are sparse, they appear adequate to conclude that the LD_{50} for oral intake of soluble uranium compounds exceeds several grams and probably exceeds 10 grams of uranium, and for inhalation intakes is at least, greater than 1 g, and likely significantly greater.

Kathren and Burklin's 1st Paper leads to:

- Conservative Recommendations:
  - Provisional LD_{50} for oral intakes 5 g
  - Provisional LD_{50} for inhalation intakes 1 g