MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Uranium (soluble forms)
CAS Numbers: Multiple
Date: July 2012
Profile Status: Draft 2, Postpublic Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 67
Species: Dog

Minimal Risk Level: 0.0001 [ ] mg/kg/day [ ] ppm [X] mg/m^3

Reference: Rothstein A. 1949a. Uranyl fluoride. In: Voegtlin C, Hodge HC, eds. Pharmacology and toxicology of uranium compounds. National Nuclear Energy Series: Manhattan Project Technical Section, Division VI, Vol 1. New York, NY: McGraw-Hill. pp. 548-560.

Experimental design: Groups of 2–6 dogs per group (strain and gender not specified) were exposed to 0.19, 2.8, or 12.2 mg/m^3 of uranyl fluoride dust (0.15, 2.2, or 9.2 mg U/m^3) for 6 hours/day, 6 days/week for 5 weeks. (Doses were analytically determined, not estimated.) The AMAD for the particles is assumed to be 1.5–2.1 μm; average 1.8 μm (see Pozzani 1949). Separate control studies were conducted (Sprague 1949) in which animals were exposed in control chambers by full or head-only exposure for a duration similar to study conditions. Clinical signs of toxicity, mortality, body weight changes, hematology, and blood and urine chemistries were monitored. At the termination of the study, the animals were sacrificed, selected organs were histopathologically examined, and uranium levels were determined.

Effect noted in study and corresponding doses: Anorexia, rhinitis, and polydipsia were observed in the two dogs exposed to 9.2 mg U/m^3; prior to death, vomiting blood, severe muscle weakness, and exhibited lassitude were observed. No deaths or clinical signs were observed at 0.15 or 2.2 mg U/m^3. Severe weight loss was also observed at 9.2 mg U/m^3; no alterations in body weight gain were observed at 0.15 or 2.2 mg U/m^3. At 9.2 mg U/m^3, both dogs had increased blood NPN levels with the maximum value over 200 mg%. At 2.2 mg U/m^3, blood NPN and urinary amino acid levels were normal while one of three dogs had increased urinary protein levels. At 9.2 mg U/m^3, severe renal damage was seen in dogs. Moderate renal damage (no additional information provided) was observed at 2.2 mg U/m^3 and very slight damage was observed in about 50% of the dogs at 0.15 mg U/m^3.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL

The study identified a LOAEL of 0.15 mg U/m^3 for minimal microscopic lesions in the renal tubules; BMD modeling was not used to estimate the point of departure because incidence data were not available for all groups.

Uncertainty Factors used in MRL derivation:

[x] 3 for use of a minimal LOAEL
[x] 10 for extrapolation from animals to humans
[x] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: Human equivalent values were not calculated because regional deposited dose ratios are not available for dogs (EPA 1994d); thus, the $LOAEL_{ADJ}$ was used as the point of departure with an uncertainty factor of 10 for extrapolation from animals to humans.

Was a conversion used from intermittent to continuous exposure? The LOAEL was adjusted for intermittent exposure:

$LOAEL_{ADJ}$ = (0.15 mg/m^3) * (6 hours/24 hours) * (6 days/7 days) = 0.032 mg/m^3

Other additional studies or pertinent information that lend support to this MRL: The toxicity of various soluble and poorly soluble uranium compounds has been tested in several animal species (Dygert 1949a, 1949b; Roberts 1949; Rothermel 1949; Rothstein 1949a; Spiegl 1949; Stokinger et al. 1953). These studies identify the kidney and respiratory tract as the most sensitive targets of uranium toxicity. The renal effects consisted of tubular degeneration and necrosis at concentrations of $\geq$0.2 mg U/m^3. Compound and species differences in toxicity were found. The more soluble compounds were more toxic and dogs and rabbits were more sensitive than rats, mice, and guinea pigs.

In addition to the renal effects, pulmonary toxicity has been observed in animals particularly after exposure to uranium hexafluoride. Exposure to 2 mg U/m^3 for 30 days resulted in severe pulmonary edema in rabbits and slight pneumonia in dogs (Spiegl 1949). At higher concentrations (13.3 mg U/m^3), lung edema, hemorrhage, and emphysema were observed in rats, rabbits, and guinea pigs (Spiegl 1949). Since uranium hexafluoride is readily hydrolyzed to uranyl fluoride and hydrogen fluoride and hydrogen fluoride is a strong respiratory irritant resulting in pulmonary edema, it is likely that the observed respiratory effects are due to the hydrogen fluoride exposure. Respiratory effects have also been observed in rabbits and rats exposed to 6.8 mg U/m^3 as ammonium diuranate (Dygert 1949b). In rabbits, ammonium diuranate exposure (6.8 mg U/m^3) resulted in extensive respiratory tract irritation, evidence by nasal bleeding and pulmonary edema, hemorrhage, and necrosis. Respiratory irritation (nasal bleeding and interstitial bronchiopneumonia) was also observed in rats exposed to 6.8 mg U/m^3. It is possible that these effects were secondary to the release of the ammonium ion, rather than uranium toxicity. Respiratory effects have not been consistently observed following exposure to other uranium compounds.

The kidney effects were observed at lower concentrations than the respiratory effects and the dogs were the most sensitive species. The lowest LOAEL values identified in dogs are 0.13 mg U/m^3 as uranyl nitrate for proteinuria (Roberts 1949) and 0.15 mg U/m^3 as uranyl fluoride for tubular damage (Rothstein 1949a). In the Roberts (1949) study, an increase in urinary protein excretion was observed between days 9 and 12 and then returned to normal; very mild histological changes which the investigator noted was not of sufficient severity to be of concern were observed in the renal cortex in two dogs exposed for 10 days. Since the two LOAEL values are almost identical, the Rothstein (1949a) study was selected as the basis of the MRL because it included histological examination of dogs exposed for an intermediate duration (the one dog examined at the end of the Roberts study had severe chronic nephritis, which masked an uranium-induced renal effects). Although the lowest LOAEL value in rats (0.13 mg U/m^3) was similar to the lowest LOAEL values in dogs, the intermediate and chronic databases for soluble uranium compounds provide strong evidence that dogs are more sensitive than rats.

Agency Contacts (Chemical Managers): Sam Keith, Obaid Faroon, Nickolette Roney, Franco Scinicariello, Sharon Wilbur