APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Uranium (insoluble forms)
CAS Numbers: Multiple
Date: July 2012
Profile Status: Draft 2, Postpublic Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 66
Species: Dog

Minimal Risk Level: 0.002 [ ] mg/kg/day [ ] ppm [X] mg/m$^3$

Reference: Rothstein A. 1949b. Uranium dioxide. 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. 614-621.

Experimental design: Groups of 6–19 dogs of unspecified strain and gender were exposed to 1.3, 9.3, or 10.4 mg/m$^3$ uranium dioxide (1.1, 8.2, or 9.2 mg U/m$^3$) 6 days/week for 5 weeks. Based on other studies conducted by this investigator (Rothermel 1949; Rothstein 1949c), it is assumed that the animals were exposed for 6 hours/day. Exposure to 8.2 mg U/m$^3$ was conducted in head-only exposure units and exposure to 1.1 or 9.2 mg U/m$^3$ were performed in full-body exposure units. The median particle size was 0.4 μm with a geometric standard deviation of 2. The following parameters were used to assess toxicity: mortality, body weight changes, standard hematology (except in the 8.2 mg U/m$^3$ group), clinical chemistry (serum nonprotein nitrogen and urea nitrogen levels), urinalysis (protein, amino acid, catalase, phosphate, and ketone levels), and histopathology. 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. Body weight, mortality, biochemical, hematological, and histopathological data were collected. Dogs (n = 6–19; unspecified sex and strain) were exposed to uranium dioxide dust at concentrations of 1.1, 8.2, or 9.2 mg U/m$^3$ for 5 weeks, 6 days/weeks, 6 hours/day. (Doses were analytically determined, not estimated.) Studies conducted at 8.2 mg U/m$^3$ were conducted in head exposure units. Studies conducted at the other concentrations were performed in full exposure units. The AMAD for the particles is assumed to be 1.5–2.1 μm; average 1.8 μm (see Pozzani 1949). Mortality, body weight changes, standard hematology (except in the 8.2 mg U/m$^3$ group), blood and urine chemistries, pathology, and uranium distribution in tissues were measured.

Effect noted in study and corresponding doses: No dogs died from exposure to uranium dioxide dust. Additionally, no alterations in body weight gain or hematology, serum clinical chemistry, or urinalysis parameters were noted. Histopathological alterations were limited to the kidneys; "very slight" renal tubular degeneration was observed in two of six dogs at 8.2 mg U/m$^3$; no alterations were observed in two dogs examined from the 9.2 mg U/m$^3$ group.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

The study identified a NOAEL of 1.1 mg U/m$^3$ and a LOAEL of 8.2 mg/m$^3$ for minimal microscopic lesions in the renal tubules. The NOAEL of 1.1 mg U/m$^3$ was used as the point of departure for the MRL; BMD modeling was not used to estimate the point of departure due to the limited reporting of incidence data.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a 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 $NOAEL_{ADJ}$ 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 NOAEL was adjusted for intermittent exposure:

$NOAEL_{ADJ}$ = (1.1 $mg/m^3$) * (6 hours/24 hours) * (6 days/7 days) = 0.24 $mg/m^3$

Other additional studies or pertinent information that lend support to this MRL: Intermediate-duration inhalation studies in animals have examined the toxicity of various insoluble uranium compounds including uranium dioxide, uranium peroxide, uranium trioxide, and triuranium octaoxide in several animal species (Dygert 1949c, 1949d; Rothstein 1949b, 1949c; Stokinger et al. 1953). The results of these studies suggest that the kidney and the respiratory tract are sensitive targets of uranium toxicity, with the kidney being the most sensitive target. Very slight renal tubular damage was observed in dogs exposed to 8.2 mg $U/m^3$ as uranium dioxide for 5 weeks (Rothstein 1949b), moderate tubular necrosis was observed in rabbits exposed to 15.4 mg $U/m^3$ as uranium peroxide for 23 days (Dygert 1949d), moderate necrosis was observed in rats, rabbits, and dogs exposed to 16 mg $U/m^3$ as uranium trioxide for 4 weeks (Rothstein 1949c), and marked tubular necrosis was observed in rabbits exposed to 19.4 mg $U/m^3$ as uranium dioxide for 5 weeks (Rothstein 1949b). Although there are limited data to make species comparisons, data for uranium dioxide suggest that rabbits are more sensitive than rats, mice, or guinea pigs; the data do not allow for a comparison between rabbits and dogs. In addition to the renal effects observed in rats, rabbits, and dogs exposed to uranium trioxide, very slight pulmonary lesions were observed in dogs and rats exposed to 16 mg $U/m^3$ and severe effects were observed in rabbits dying early after exposure to 16 mg $U/m^3$ (Rothstein 1949c). Additionally, the results of the Rothstein (1949b) study which is the basis of the MRL are supported by the findings of slight to mild tubular degeneration in dogs exposed to 10 mg $U/m^3$ as uranium dioxide for 1 year; no effects were observed at 1 mg $U/m^3$ (Stokinger et al. 1953).

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