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 [ ] Intermediate [X] Chronic
Graph Key: 92
Species: Monkey

Minimal Risk Level: 0.0008 [ ] mg/kg/day [ ] ppm [X] mg/m^3

Reference: Leach LJ, Maynard EA, Hodge HC, et al. 1970. A five-year inhalation study with natural uranium dioxide (UO_2) dust. I. Retention and biological effects in the monkey, dog, and rat. Health Physics 18:599-612.

Leach LJ, Yuile CL, Hodge HC, et al. 1973. A five-year inhalation study with natural uranium dioxide (UO_2) dust. II. Postexposure retention and biologic effects in the monkey, dog, and rat. Health Physics 25: 239-258.

Experimental design: Rhesus monkeys (5 males, 20 females) were exposed to 5.8 mg/m^3 uranium dioxide (5.1 mg U/m^3) 5.4 hours/day, 5 days/week for 5 years; the mass median particle diameter was 1.03 µm with a geometric standard deviation of 2.40. Another group of one male and five female monkeys served as controls. Groups of 1–2 monkeys were killed after 1 day, 4 days, 15 days, 1 month, 2 months, 3 months, 5 months, 1 year, 1.5 years, 1.8 years, 1.9 years, 3.6 years, 4.1 years, or 4.7 years; two monkeys were killed at 5 years. Six monkeys were observed for 6.5 years after exposure termination; two were killed after 12 months, one after 6 years, and three after 6.5 years; the results of the recovery period examinations were reported in Leach et al. (1973). The following parameters were used to assess toxicity: general health, body weight, peripheral hematology, blood NPN levels, and histopathology of major tissues and organs. No uranium dioxide-related deaths were observed.

Effect noted in study and corresponding doses: No alterations in body weight, hematological parameters, or blood NPN levels were found. Histological alterations were limited to the lungs and tracheobronchial lymph nodes. After 2–3 months of exposure, granular black pigment accumulations were found in the lungs and tracheobronchial lymph nodes. After 3.6 years of exposure, slight fibrosis was observed in the lungs and hyaline fibrosis was observed in the tracheobronchial lymph nodes; the severity of the fibrosis increased with exposure duration and was not observed in the controls. Fibrosis was still present in the lungs and tracheobronchial lymph nodes 6.5 years postexposure.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL

The study identified a LOAEL of 5.1 mg U/m^3 for fibrosis in the lungs and tracheobronchial lymph nodes; BMD modeling was not used due to the small number of animals sacrificed at each time period.

Uncertainty Factors used in MRL derivation:

[x] 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 monkeys (EPA 1994d). 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:

$LOAEL_{ADJ}$ = (5.1 mg U/m^3) * (5.4 hours/24 hours) * (5 days/7 days) = 0.82 mg U/m^3

Other additional studies or pertinent information that lend support to this MRL: There are limited data available to assess the toxicity of chronic exposure to insoluble uranium compounds. Slight to mild renal tubular degeneration was observed in dogs exposed to 10 mg U/m^3 as uranium dioxide for 1 year (Stokinger et al. 1953); no alterations were observed at 1 mg U/m^3. Although several tissues were examined histologically, significant alterations were only noted for the kidneys. Stokinger et al. (1953) also exposed rats to 1 or 10 mg U/m^3 as uranium dioxide, but no uranium-related alterations were observed. In a second chronic duration study, no adverse effects were observed in rats or dogs exposed to 5.1 mg U/m^3 as uranium dioxide for 1–5 years (Leach et al. 1970). However, fibrosis in the tracheobronchial lymph nodes and fibrosis and metaplasia in the lungs were observed in dogs during a 6.5-year postexposure period (Leach et al. 1973). In monkeys, exposure to 5.1 mg U/m^3 resulted in lung fibrosis beginning after 3.6 years of exposure (Leach et al. 1970); the severity of the fibrosis increased with exposure duration. Fibrosis was also present in the lungs and tracheobronchial lymph nodes in monkeys sacrificed during the 6.5-year postexposure period (Leach et al. 1973). The investigators noted that the fibrosis may have been a radiotoxic effect based on the magnitude of the radiation dose, the absence of renal effects, and the similarity of the lesions to those observed following exposure to plutonium dioxide; the alpha-radiation tissue doses were >500 rad (5 Gy) for the lungs and 7,000 rad (70 Gy) for the lymph nodes. However, it is unclear whether the damage was chemically or radiologically induced (or both); similar degenerative effects in the lungs have also been observed following prolonged exposure to diverse inorganic dusts. An elevation of blood nonprotein nitrogen level was also observed in the monkeys during the postexposure period, but no histological alterations were observed in the kidneys (Leach et al. 1973).

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