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 [ ] Intermediate [X] Chronic
Graph Key: 100
Species: Dog

Minimal Risk Level: 0.00004 [ ] mg/kg/day [ ] ppm [X] mg/m^3

Reference: Stokinger HC, Baxter RC, Dygert HP, et al. 1953. Uranium Tetrachloride: Toxicity following inhalation for 1 and 2 years. 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. 1522-1553.

Experimental design: Dogs of both sexes (11–12 males, 9–10 females) were exposed to uranium tetrachloride in inhalation chambers for 33 hours/week for 1 year at concentrations of 0.05 and 0.20 mg U/m^3. (Doses were analytically determined, not estimated.) A control group of five male and seven female dogs were similar exposed to chamber air in a separate experiment. The size-mass median particle size of uranium tetrachloride dust was 1.58 µm (range of 1.19–2.21 µm; geometric standard deviation of 2.24) for the 0.05 mg U/m^3 exposures and 1.83 µm (range of 1.07–3.35 µm; geometric standard deviation of 2.25) for the 0.2 mg U/m^3 exposures. The animals were monitored for body weight alterations, clinical signs of toxicity, and biochemical alterations in the blood and urine. At the termination of the study, the animals were sacrificed and selected organs were histopathologically examined.

Effect noted in study and corresponding doses: All dogs survived the 1-year exposure period. No alterations in body weight gain, hematological parameters, or blood NPN levels were observed. Urinary protein levels were elevated, as compared to controls; however, pre-exposure levels were also elevated, precluding evaluating the clinical significance of the effect. Alterations in bromsulfalein retention test, indicating impaired liver function, were observed in the four dogs tested (0.2 mg U/m^3 group); no alterations in blood clotting times were observed. In the absence of histological evidence of liver damage, the change was not considered clinically significant. Renal tubular atrophy was observed in 2/16 dogs exposed to 0.05 mg U/m^3 (not statistically significant using Fisher Exact test). Slight tubular atrophy in the inner cortex was observed in 7/14 dogs exposed to 0.2 mg U/m^3.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] $BMCL_{10}$ 0.019 mg U/m^3 for renal toxicity

Data for the incidence of renal tubular atrophy were analyzed using all available dichotomous models in the EPA BMDS (version 2.1.2) using the extra risk option. The multistage model was run for all polynomial degrees up to n-1 (where n is the number of dose groups including control). Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all of the models meeting adequate fit criteria, the BMCL from the model with the lowest Akaike Information Criteria (AIC) was chosen. BMCs and lower bounds on the BMC (BMCLs) associated with a BMR of 10% extra risk were calculated for all models and are presented in

Table A-1. As assessed by the chi-square goodness-of-fit statistic, all of the models provided adequate fit to the data. The BMCs ranged from 0.032 to 0.082 mg U/m^3 and the BMCLs ranged from 0.019 to 0.054 mg U/m^3. The quantal-linear and the multistage (1-degree polynomial) had the lowest AIC values; the $BMCL_{10}$ of 0.019 mg U/m^3 estimated for both models was selected as a point of departure. The fit of the quantal-linear model is presented in Figure A-1.

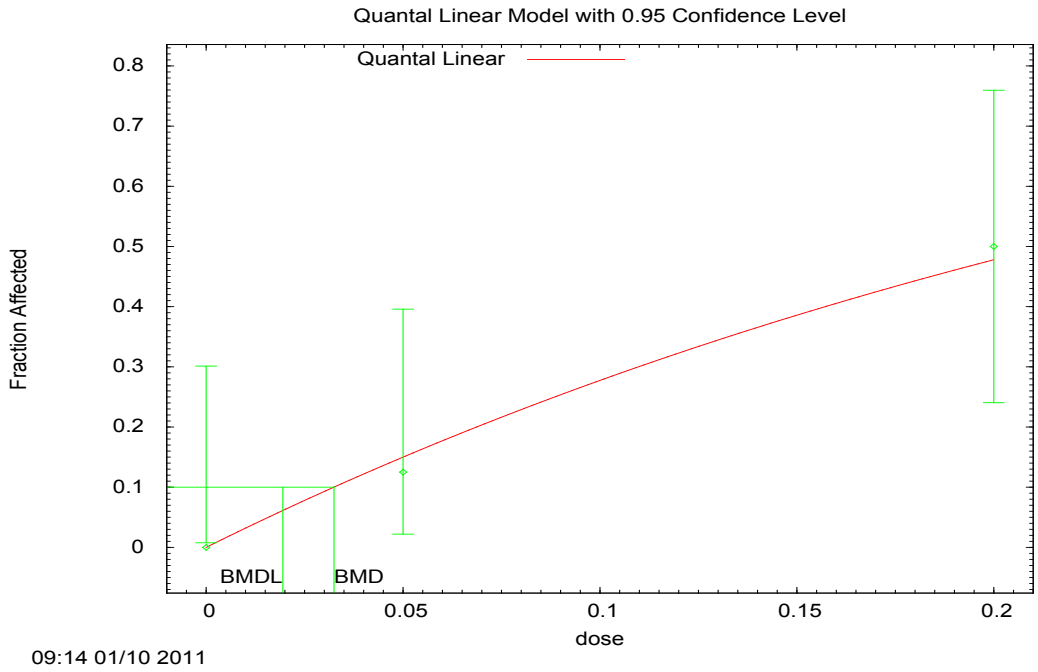
Table A-1. Model Predictions for the Incidence of Renal Tubular Atrophy in Dogs Exposed to Uranium Tetrachloride for 1 Year (Stokinger et al. 1953)

Model	χ^2 Goodness-of-fit	p-value[a]	AIC	BMC_{10} (mg U/m^3)	$BMCL_{10}$ (mg U/m^3)
Gamma[b]	35.4648	1	35.4648	0.0411568	0.0196557
Logistic	36.7375	0.3616	36.7375	0.0825225	0.054177
Log Logistic	35.4648	1	35.4648	0.0418036	0.0146656
Log Probit	35.4648	1	35.4648	0.0426877	0.00300431
Multistage (1 degree polynomial)	35.4648	**0.9485**	**33.5743**	**0.0324681**	**0.019467**
Multistage (2 degree polynomial)	33.5743	1	35.4648	0.0402323	0.0196557
Probit	36.5663	0.3921	36.5663	0.0756112	0.0502782
Weibull[b]	35.4648	1	35.4648	0.0409589	0.0196557
Quantal-Linear	33.5743	**0.9485**	**33.5743**	**0.0324681**	**0.019467**

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.

AIC = Akaike Information Criteria; BMC = benchmark concentration associated with the selected benchmark response of 10% extra risk; BMCL = 95% lower confidence limit on the BMC

Figure A-1. Predicted (Quantal-Linear Model) and Observed Incidence of Renal Tubular Atrophy*



*BMC and BMCL indicated are associated with 10% extra risk and are in units of mg U/m^3.

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). The $BMCL_{ADJ}$ 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 BMCL was adjusted for intermittent exposure:

$BMCL_{ADJ}$ = (0.019 mg U/m^3) * (33 hours/168 hours) = 0.0037 mg U/m^3

Other additional studies or pertinent information that lend support to this MRL: There are limited human data on the chronic toxicity of soluble uranium. Thun et al. (1985) examined uranium mill workers exposed to yellowcake (26–86% ammonium diuranate), which was considered biologically soluble, for at least 1 year. Significant increases in urinary excretion of β_2-microglobulin and amino acids were observed in the uranium workers, suggesting impaired renal tubular function. Clearance of β-2-microglobulin relative to that of creatinine was significantly associated with the length of time that

the uranium workers had spent in the yellowcake area. Although urinary uranium levels were reported, atmospheric concentrations were not reported.

Stokinger et al. (1953) examined the chronic toxicity of uranium hexafluoride, uranium tetrachloride, and uranyl nitrate in dogs and rats following a 1-year exposure. Slight to mild renal tubular atrophy was observed in dogs and rats exposed to 0.2 mg U/m^3 as uranium hexafluoride or uranium tetrachloride; no effects were observed at 0.05 mg U/m^3. Exposure to uranyl nitrate resulted in mild to moderate tubular atrophy in dogs exposed to 0.25 mg U/m^3 (NOAEL of 0.15 mg U/m^3) and mild to marked tubular atrophy in rats exposed to 2 mg U/m^3 (NOAEL of 0.25 mg U/m^3).

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