APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach or the benchmark dose level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30333.

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).

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

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.

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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

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.

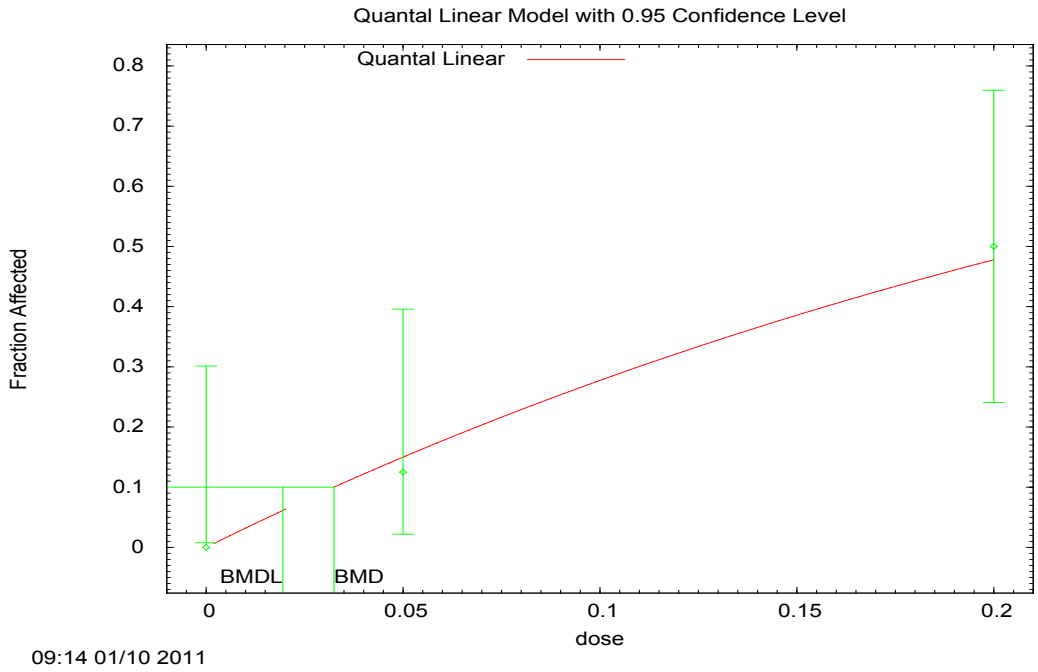
Table A-1. Model Predictions for the Incidence of Renal Tubular Atrophy in Dogs Exposed to Uranium Tetrachloride for 1 Year (Stokinger et al. 1953)

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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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Uranium (soluble forms)
CAS Numbers: Multiple
Date: July 2012
Profile Status: Draft 2, Postpublic Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 14
Species: Mouse

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

Reference: Domingo JL, Paternain JL, Llobet JM, et al. 1989c. The developmental toxicity of uranium in mice. Toxicology 55:143-152.

Experimental design: Groups of 20 pregnant Swiss mice were administered via gavage 0, 5, 10, 25, or 50 mg/kg/day uranyl acetate dihydrate (0, 2.8, 5.6, 14, or 28 mg U/kg/day) on gestation days 6–15. Body weights, food consumption, and general appearance were monitored daily. At termination, maternal liver and kidney weights were measured and uterine contents (number of implantation sites, resorptions, dead fetuses, and live fetuses) were evaluated. Live fetuses were evaluated for body weight, body length, sex, gross morphological abnormalities, visceral malformations, visceral anomalies (evaluated in 1/3 of fetuses), and skeletal defects (evaluated in 2/3 of fetuses).

Effect noted in study and corresponding doses: Significant decreases in maternal body weight were observed in all uranium groups; during the exposure period, the dams in the 2.6, 5.6, 14, and 28 mg U/kg/day groups weighed 33, 53, 75, and 88% less than controls, respectively. Significant decreases in food intake were also observed in the dams exposed to ≥5.6 mg U/kg/day. A significant decrease in the number of live fetuses was observed at 5.6 mg U/kg/day, but was not observed at the two higher dose levels. No significant alterations in the number of early or late resorptions, number of dead fetuses, or sex ratio were observed. Significant decreases in fetal body weight were observed at ≥2.8 mg U/kg/day and decreases in fetal length were observed at ≥5.6 mg U/kg/day. Significant increases in the incidences of external defects were observed at 2.8 mg U/kg/day. The alterations included cleft palate (significant at ≥5.6 mg U/kg/day) and hematomas (significant at 2.8 and 28 mg U/kg/day). The total number of skeletal defects was significantly increased at 14 and 28 mg U/kg/day; skeletal defects included bipartite sternebrae (significant at 2.8, 14, and 28 mg U/kg/day), some metatarsal of hindlimb poorly ossified (significant at 14 and 28 mg U/kg/day), delayed ossification of skull (significant at 14 and 28 mg U/kg/day), and caudal reduced ossification (significant at 14 and 28 mg U/kg/day).

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMDL 0.2 mg U/kg/day for developmental toxicity

The results of the Domingo et al. (1989c) study suggest maternal body weight gain and fetal body weight and external and skeletal alterations as sensitive end points of uranium toxicity. It is possible that the developmental effects were secondary to the maternal toxicity; however, some of these effects may also be primary effects of uranium on the developing fetus. BMD modeling was used to identify potential points of departure for maternal and fetal end points. The maternal end point was decreased maternal body weight gain and the fetal end points included decreased fetal body weights and external and skeletal alterations. As summarized in Table A-2, there were significant increases in the incidence of litters with a particular types of external defect or skeletal defect and increases in the total number of litters with

external or skeletal defects. At all but the lowest dose tested, the increase in the incidence of external defects was primarily due to increases in the incidence of cleft palate. The incidence of hematomas does not appear to be dose-related. Thus, only the incidence of cleft palate was considered for BMD modeling. The skeletal defects consisted of increases in the incidence of bipartite sternebrae and reduced or delayed ossification in several locations (skull, caudal, hindlimb metatarsals, and proximal phalanges). Unfortunately, the investigators did not provide the information on the total number of litters with reduced or delayed ossification. To estimate potential points of departure for skeletal defects, the incidence data for bipartite sternebrae and the total incidence of skeletal defects were modeled.

Table A-2. Incidence of Litters with External or Skeletal Defects

Dose level (mg U/kg/day)	0	2.8	5.6	14	28
Number of litters	18	17	18	18	18
Cleft palate	0	2 (12%)	13[a] (72%)	13[a] (72%)	16[a] (89%)
Hematomas (dorsal or in facial area)	0	6[b] (35%)	2 (11%)	4 (22%)	8[b] (44%)
Total external defects	0	8[c] (47%)	14[a] (78%)	14[a] (78%)	17[b] (94%)
Bipartite sternebrae	0	6[c] (35%)	3 (17%)	9[a] (50%)	13[a] (72%)
Poor ossification of hindlimb metatarsal	4 (22%)	9 (53%)	15 (83%)	18[b] (100%)	18[a] (100%)
Poor ossification of proximal phalanges	2 (11%)	0	6 (33%)	13[b] (72%)	14[b] (78%)
Delayed skull ossification	0	0	3 (17%)	9[c] (50%)	12[c] (67%)
Reduced caudal ossification	4 (22%)	9 (53%)	12 (67%)	18[b] (100%)	18[b] (100%)
Total skeletal defects	4 (22%)	11 (65%)	15 (83%)	18[c] (100%)	18[c] (100%)

[a]Significantly different from controls ($p<0.01$).
[b]Significantly different from controls ($p<0.001$).
[c]Significantly different from controls ($p<0.05$).

Source: Domingo et al. 1989c

Data for the number of litters with cleft palate, bipartite sternebrae, and total skeletal defects (summarized in Table A-2) 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 BMR. For a given end point, the BMDL from the model with the lowest AIC (among all of the models meeting adequate fit criteria) was chosen. BMDs and lower bounds on the BMD (BMDLs) associated with a BMR of 5% extra risk for dichotomous data were calculated for all models and are presented in Table A-3.

Table A-3. Model Predictions for Developmental Effects in the Offspring of Mice Administered Uranyl Acetate via Gavage on Gestation Days 6–15 (Domingo et al. 1989c)

Model	AIC	χ^2 Goodness-of-fit	p-value[a]	BMD_{05} (mg U/kg/day)	$BMDL_{05}$ (mg U/kg/day)
Cleft palate					
Gamma[b]	78.21	8.69	0.0693	ND (GF)	ND (GF)
Logistic	92.12	18.44	0.0004	ND (GF)	ND (GF)
Log Logistic	**77.98**	**6.15**	**0.1047**	**0.75**	**0.20**
Log Probit	76.56	7.06	0.133	ND (LSR)	ND (LSR)
Multistage (1 degree polynomial)	78.21	8.69	0.0693	ND (GF)	ND (GF)
Multistage (2 degree polynomial)	78.21	8.69	0.0693	ND (GF)	ND (GF)
Multistage (3 degree polynomial)	78.21	8.69	0.0693	ND (GF)	ND (GF)
Multistage (4 degree polynomial)	78.21	8.69	0.0693	ND (GF)	ND (GF)
Probit	92.80	18.94	0.0003	ND (GF)	ND (GF)
Weibull[b]	78.21	8.69	0.0693	ND (GF)	ND (GF)
Quantal-Linear	78.58	8.4	0.078	ND (GF)	ND (GF)
Total skeletal defects					
Gamma[b]	63.69	0.24	0.889	0.39	0.12
Logistic	**61.85**	**0.46**	0.9275	**0.37**	**0.25**
Log Logistic	64.42	0.77	0.6808	0.84	0.12
Log Probit	64.02	0.49	0.7828	0.85	0.30
Multistage (1 degree polynomial)	61.87	0.29	0.9617	0.17	0.12
Multistage (2 degree polynomial)	63.54	0.14	0.9326	0.23	0.12
Multistage (3 degree polynomial)	63.45	0.07	0.9653	0.20	0.12
Multistage (4 degree polynomial)	63.40	0.03	0.9848	0.19	0.12
Probit	61.86	0.49	0.9205	0.36	0.26
Weibull[b]	63.64	0.21	0.902	0.33	0.12
Quantal-Linear	61.87	0.29	0.9617	0.17	0.12

Table A-3. Model Predictions for Developmental Effects in the Offspring of Mice Administered Uranyl Acetate via Gavage on Gestation Days 6–15 (Domingo et al. 1989c)

Model	AIC	χ^2 Goodness-of-fit	p-value[a]	BMD_{05} (mg U/kg/day)	$BMDL_{05}$ (mg U/kg/day)
Bipartite sternebrae					
Gamma[b]	94.61	7.49	0.0578	ND (GF)	ND (GF)
Logistic	97.86	7.44	0.0591	ND (GF)	ND (GF)
Log Logistic	**93.02**	**4.37**	**0.224**	**0.64**	**0.42**
Log Probit	97.82	8.65	0.0343	ND (GF)	ND (GF)
Multistage (1 degree polynomial)	94.61	7.49	0.0578	ND (GF)	ND (GF)
Multistage (2 degree polynomial)	94.61	7.49	0.0578	ND (GF)	ND (GF)
Multistage (3 degree polynomial)	94.61	7.49	0.0578	ND (GF)	ND (GF)
Multistage (4 degree polynomial)	94.61	7.49	0.0578	ND (GF)	ND (GF)
Probit	97.69	7.43	0.0595	2.80	2.11
Weibull[b]	94.61	7.49	0.0578	ND (GF)	ND (GF)
Quantal-Linear	94.61	7.49	0.0578	ND (GF)	ND (GF)

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

AIC = Akaike Information Criteria; BMD = benchmark dose associated with the selected benchmark response of 5% extra risk; BMDL = 95% lower confidence limit on the BMC ND (GF) = not determined, goodness-of-fit criteria <0.10; ND (LSR) = not determined, largest scaled residual >2

The fetal body weight data and the maternal body weight gain data, summarized in Table A-4 were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS, version 2.1.2). The following procedure for fitting continuous data was used: the simplest model (linear) was first applied to the data while assuming constant variance; if the data were consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data while assuming constant variance. 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 BMR. Among all of the models providing adequate fit to the data, the BMDL from the model with the lowest AIC was chosen. If the test for constant variance was negative, then the linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data and evaluated while the variance model was applied. Model fit and point of departure selection proceeded as described earlier. If the test for constant variance was negative and the nonhomogenous variance model did not provide an adequate fit to the variance data, then the data set was considered unsuitable for modeling. For all fetal body weight models, a BMR of 5% relative deviation was used; a BMR of 10% was used for all maternal body weight gain models. Although the Hill model with constant variance or nonconstant variance

provided an adequate fit to means for the fetal body weight data, the models did not provide adequate fit to the variance and were not considered suitable for identifying a point of departure for an MRL. None of the available models provided adequate fit for the maternal body weight gain data.

Table A-4. Maternal Body Weight Gain and Fetal Body Weights

Dose level (mg U/kg/day)	0	2.8	5.6	14	28
Maternal body weight gain on gestation days 6-15 (g) ±standard deviation	14.5±6.6	9.7±1.8[a]	6.8±9.5[a]	3.6±8.4[b]	1.8±6.2[c]
Fetal body weight (g) ±standard deviation	1.40±0.15	1.04±0.25[a]	0.93±0.24[a]	0.84±0.11[a]	0.77±0.17[a]

[a]Significantly different from controls ($p<0.001$).
[b]Significantly different from controls ($p<0.05$).
[c]Significantly different from controls ($p<0.01$).

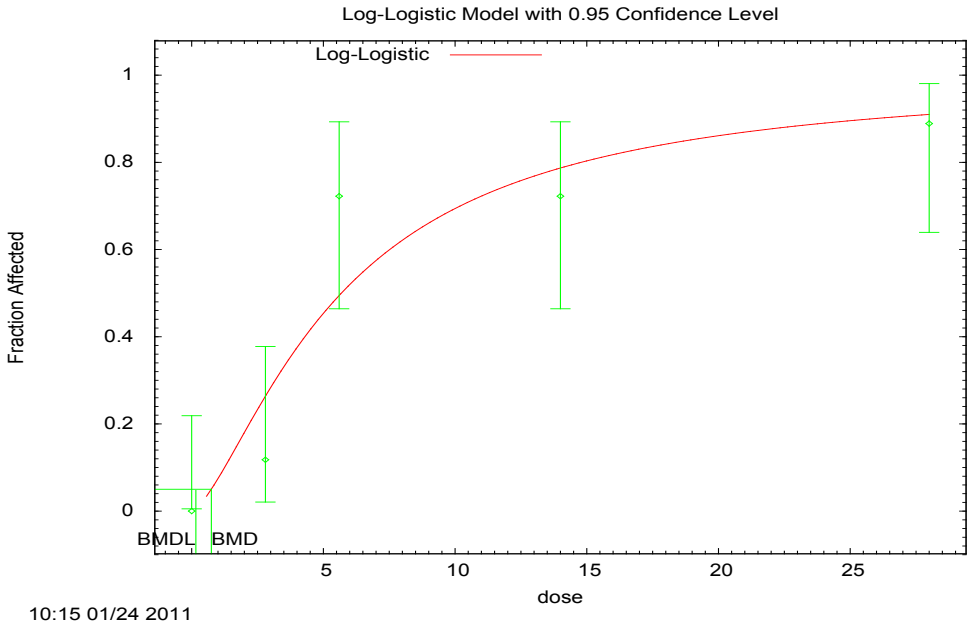
Source: Domingo et al. 1989c

The potential points of departure for the acute-duration oral MRL are summarized in Table A-5. The $BMDL_{05}$ values for external and skeletal defects ranged from 0.20 to 0.42 mg U/kg/day and the LOAEL value for the maternal and fetal body weight effects was 2.8 mg U/kg/day. The $BMDL_{05}$ of 0.20 mg U/kg/day for cleft palate was selected as the basis of the MRL. Because this value is lower than the other potential points of departure, it is likely to be protective for these effects. The fit of the log logistics model to the cleft palate data is presented in Figure A-2.

Table A-5. Summary of Potential Points of Departure for an Acute-Duration Oral MRL

Effect	Point of departure (mg U/kg/day)	Source
Cleft palate	0.20	$BMDL_{05}$ (log logistic model)
Total skeletal defects	0.25	$BMDL_{05}$ (logistic model)
Bipartite sternebrae	0.42	$BMDL_{05}$ (log logistic model)
Fetal body weight	0.28	LOAEL/uncertainty factor of 10
Maternal body weight gain	0.28	LOAEL/uncertainty factor of 10

Figure A-2. Predicted (Log Logistic Model) and Observed Incidence of Cleft Palate*



*BMD and BMDL indicated are associated with 5% extra risk and are in units of mg U/kg/day.

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? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: There are limited human data on the oral toxicity of uranium. Signs of gastrointestinal irritation (nausea, vomiting, diarrhea) were observed in a subject ingesting 14.3 mg U/kg as uranyl nitrate in drinking water (Butterworth 1955); other potential targets of toxicity were not examined. Acute oral exposure studies in rats and mice have examined the lethality, systemic toxicity, neurotoxicity, and developmental toxicity of uranium. Information on the systemic toxicity is limited to two single-exposure toxicity study in rats (Domingo et al. 1987) and mice (Martinez et al. 2003) administered lethal doses and a repeated exposure study in mice (Ozmen and Yurekli 1998). In the 2 weeks following administration of a single gavage dose of 118 mg U/kg as uranyl acetate to rats, significant increases in urine volume (in the absence of changes in water consumption), plasma creatinine and urea, and urinary total protein and creatinine were observed; hyperemia and microhemorrhagic foci were also observed in the liver and kidneys at the end of the 2-week observation period (Domingo et al. 1987). In mice, administration of 166 mg U/kg as uranyl nitrate resulted in increases in blood urea and creatinine levels and proximal tubular necrosis (Martinez et

al. 2003). Similarly, significant increases in BUN and creatinine levels were observed in mice exposed to 508 mg U/kg/day as uranyl acetate in the diet for 5 days (Ozmen and Yurekli 1998); the study did not include a histological examination of the kidney or other tissues. Neurological effects consisted of increased motor activity (Briner and Murray 2005) and increased open field activity (Briner 2009) in mice administered 28 or 6 mg U/kg/day, respectively, as depleted uranyl acetate in drinking water for 2 weeks; exposure to 28 mg U/kg/day also resulted in a 53% decrease in body weight gain. Gestational exposure to ≥2.8 mg U/kg/day as uranyl acetate resulted in significant decreases in fetal body weights and increases in the occurrence hematomas in the fetuses of mice exposed on gestation days 6–15 (Domingo et al. 1989a); increases in the incidence of cleft palate were observed at ≥5.6 mg U/kg/day. Decreases in maternal body weight gain were observed at ≥2.8 mg U/kg/day. Exposure of neonatal rats (1 or 7 days of age) to 42.7 mg U/kg/day as uranyl nitrate administered via gavage in water, resulted in significant reductions in bone formation, increases in bone resorption, and diminished tooth development (Pujadas Bigi et al. 2003).

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Uranium (soluble forms)
CAS Numbers: Multiple
Date: July 2012
Profile Status: Draft 2, Postpublic Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 39
Species: Rat

Minimal Risk Level: 0.0002 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Gilman AP, Villeneuve DC, Secours VE, et al. 1998a. Uranyl nitrate 28-day and 91-day toxicity studies in the Sprague-Dawley rat. Toxicol Sci 41(1):117-128.

Experimental design: Five groups of Sprague-Dawley rats (15/sex/dose, 60 g) were exposed to uranium as uranyl nitrate in drinking water (0, 0.96, 4.8, 24, 120, and 600 mg/L) for 91 days. Time-weighted average doses calculated by the authors from fluid intake data were <0.0001 (control group), 0.06, 0.31, 1.52, 7.54, and 36.73 mg U/kg/day in males and <0.0001 (control), 0.09, 0.42, 2.01, 9.98, and 53.56 mg U/kg/day in females. Clinical signs were monitored daily and body weights were measured weekly; fluid intake and feed consumption were also measured, but the frequency was not reported. Hematological parameters serum clinical chemistry (sodium, potassium, phosphate, bilirubin, alkaline phosphatase, aspirate aminotransferase, total protein, calcium, cholesterol, glucose, uric acid, lactate dehydrogenase, sorbitol dehydrogenase), organ weights, and histopathology (tissues examined: adrenal, brain [three sections], bone marrow, bronchi, colon, duodenum, epididymis, stomach [gastric cardia, fundus, and pylorus], heart, kidney, liver, lungs, mesenteric and mediastinal lymph nodes, ovary, pancreas, parathyroid, pituitary, salivary glands, skeletal muscle, spleen, testes, thoracic aorta, thymus, thyroid, trachea, and uterus) were assessed at termination. Uranium residues were measured in samples of brain, liver, spleen, liver, kidney, and bone in the control and two highest dose groups.

Effect noted in study and corresponding doses: Hematological and biochemical parameters were not affected in a significant exposure-related manner. Statistically significant increases in renal lesions included cytoplasmic vacuolization (0/15, 9/15, 7/15, 12/15, 9/15, 7/15), tubular dilation (0/15, 4/15, 5/15, 10/15, 4/15, 5/15), and lymphoid cuffing (0/15, 6/15, 6/15, 2/15, 7/15, 10/15) in males at ≥0.06 mg U/kg/day; capsular sclerosis (0/15, 5/15, 4/15, 3/15, 6/14, 5/14), tubular anisokaryosis (0/15, 5/15, 4/15, 3/15, 6/14, 5/14; not significant at 2.01 mg U/kg/day), and interstitial reticulin sclerosis (1/15, 9/15, 8/15, 7/15, 6/14, 5/14) in females at ≥0.09 mg U/kg/day; nuclear vesiculation in males (0/15, 6/15, 10/15, 6/15, 8/15) and females (0/15, 6/15, 6/15, 7/15, 4/14, 7/14) at ≥0.06/0.09 mg U/kg/day; and glomerular adhesions (2/15, 4/15, 10/15, 10/15, 10/15, 11/15) and cytoplasmic degeneration (0/15, 2/15, 11/15, 13/15, 7/15, 7/15) in males at ≥0.31 mg U/kg/day. Lesions were also observed in the liver at all doses including anisokaryosis, vesiculation, increased portal density, perivenous vacuolation, and homogeneity; the investigators considered these adaptive and likely reversible. Thyroid lesions were observed in both sexes (multifocal reduction of follicular size, increased epithelial height in males at 0.31 mg/kg/day and females at 2.01 mg/kg/day). A decreased amount and density of colloid in the thyroid was observed in males only. Sinus hyperplasia of the spleen was observed in males and females at 36.73/53.56 mg/kg/day.

Dose and end point used for MRL derivation: 0.06 mg U/kg/day, renal toxicity. This is considered a minimal LOAEL.

[ ] NOAEL [X] LOAEL

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? No, doses were calculated by the authors on the basis of measured water intake.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: No studies have been identified that examined the toxicity of uranium in humans following an intermediate-duration oral exposure. A number of studies have examined the intermediate-duration oral toxicity of uranium in laboratory animals. Most of these studies involved exposure to soluble uranium compounds such as uranyl nitrate and uranyl acetate; there are limited data on moderately soluble or insoluble uranium compounds. The available data suggest that the kidney is the most sensitive target of uranium toxicity; at higher dose levels, neurological, reproductive, and developmental effects have been reported. At lower concentrations, histological alterations have been observed in the proximal tubules, glomerulus, and/or renal interstitium in rats and mice exposed to uranyl nitrate in drinking water (Berradi et al. 2008; Gilman et al. 1998a, 1998b, 1998c; McDonald-Taylor et al. 1992, 1997). At higher concentrations (40.38 mg U/kg/day), evidence of renal dysfunction (e.g., glycosuria, proteinuria) has also been observed (Gilman et al. 1998c). The Gilman et al. (1998a, 1998b) studies identified the LOAELs of 0.06 and 0.05 mg U/kg/day for renal effects in rats and rabbits, respectively; neither study identified NOAEL values.

The LOAELs for neurological, reproductive, and developmental effects are similar and are about 50-fold higher than the LOAEL for renal effects. Neurological effects such as sleep and behavior alterations and decreased spatial memory were observed in rats exposed to 2.5–2.7 mg U/kg/day as enriched uranyl nitrate (Houpert et al. 2005, 2007b). However, no neurological effects were observed in rats similarly exposed to the same dose of depleted uranyl nitrate (Houpert et al. 2005). The investigators suggest that the observed effects may have been related to radiological activity. The reproductive effects consisted of decreases in male fertility in rats and mice following exposure to ≥5.6 mg U/kg/day as uranyl acetate (Linares et al. 2005; Llobet et al. 1991) and alterations in ovarian folliculogenesis in mice at ≥1.25 mg U/kg/day as uranyl nitrate (Arnault et al. 2008; Feugier et al. 2008; Kundt et al. 2009). A recent study by Raymond-Whish et al. (2007) also reported alterations in ovarian folliculogenesis in mice, but the effects were at an extremely low dose (0.00039 mg U/kg/day). Additional data are needed to support whether reproductive effects occur at this dose level and to evaluate the toxicological significance of the observed effect (reduced number of small primary follicles, but no effect on primordial, secondary/growing, healthy, or atretic follicle populations). Developmental effects have been observed in rats and mice; most effects occurred at maternally toxic doses. The observed effects included neurobehavioral effects in the offspring of rats exposed premating and during gestation and lactation to 4.3 mg U/kg/day as enriched uranyl nitrate (Houpert et al. 2007a), decreases in pup body weight at ≥2.8 mg U/kg/day as uranyl acetate (Paternain et al. 1989; Sanchez et al. 2006), decreases in litter size, live fetuses, or viability at ≥14 mg

U/kg/day as uranyl acetate (Domingo et al. 1989b; Paternain et al. 1989), and altered ovarian folliculogenesis in 3-month-old pups of dams exposed to 1.25 mg U/kg/day as uranyl nitrate (Arnault et al. 2008).

The LOAELs of 0.05 and 0.06 mg U/kg/day for kidney effects in rats and rabbits (Gilman et al. 1998a, 1998b) were considered as possible points of departure for an intermediate-duration oral MRL for soluble uranium compounds. Although the rabbit study identified the slightly lower LOAEL, the rat LOAEL was selected as the point of departure for the MRL due to possible subclinical infection in the rabbits. Gilman et al. (1998b, 1998c) conducted two 91-day studies in rabbits. The kidney uranium levels for the two studies were not comparable; rabbits in the first study (Gilman et al. 1998b) had higher kidney uranium levels than in the second study (Gilman et al. 1998c) even though the dose was lower in the first study (28.70 mg U/kg/day dose and 4.98 µg U/g kidney level in the Gilman et al. 1998b study compared to 40.98 mg U/kg/day dose and 3.48 µg U/g kidney level in the Gilman et al. 1998c study). In the Gilman et al. (1998b) study, the male rabbits were not SPF derived and four animals developed *Pasteurella multocida* infections during the study; Gilman et al. (1998c) suggested that even though the affected rabbits were removed from the study, it is possible that other animals had a subclinical infection and that this may have increased sensitivity. Thus, the rat study was selected as the basis of the MRL; the rats used in the Gilman et al. (1998a) study were SPF derived. The Raymond-Whish et al. (2007) study was not selected as the point of departure because there are no other data to support this extremely low value and the toxicological significance of this slight change in one follicle population is not known.

Other Issues

The results of a serial study in which rats were exposed to several doses of uranyl nitrate in the diet for up to one year (Maynard et al. 1953) coupled with the rat 2-year study (Maynard and Hodge 1949; Maynard et al. 1953) suggest that at low exposures the renal tubular epithelium is regenerated and continued exposure does not result in more severe effects. However, at higher doses, the capacity to regenerate the renal tubular epithelium is exceeded and tubular atrophy is observed. In the serial study (Maynard et al. 1953), exposure to 170 mg U/kg/day as uranyl nitrate in the diet resulted in regeneration of the renal tubular epithelium after 2 weeks of exposure; there was no progression of renal damage with continued exposure and the renal tubules in rats exposed for 2 weeks were similar to those exposed for 1 year. Additionally, a 2 year exposure to 170 mg U/kg/day did not result in any further damage to the kidneys (Maynard and Hodge 1949; Maynard et al. 1953). In contrast, regeneration was observed in the first month of the exposure to 660 mg U/kg/day, however, with continued exposure, tubular atrophy was observed at 6–8 weeks. The severity of the atrophy and the areas of the kidney affected by uranium increased with duration. Given these data on the ability of the kidney to repair renal damage at low doses, the intermediate-duration oral MRL may be protective for chronic exposures.

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

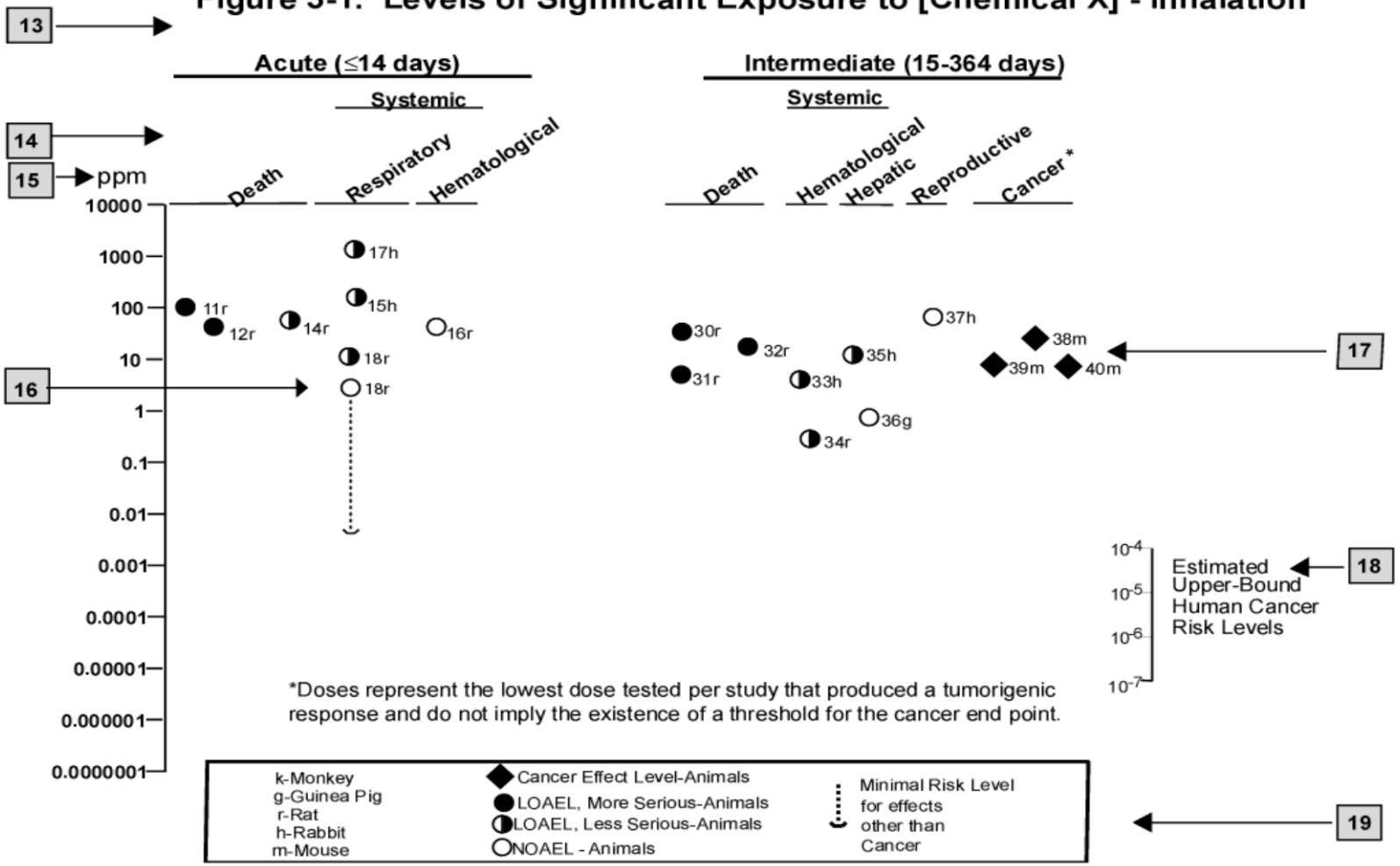
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AMAD	activity median aerodynamic diameter
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMC	benchmark concentration
BMCL	lower 95% confidence limit on the BMC
$BMCL_{05}$	BMCL associated with a BMR of 5%
$BMCL_{10}$	BMCL associated with a BMR of 10%
BMD	benchmark dose
BMDL	lower 95% confidence limit on the BMD
$BMDL_{05}$	BMDCL associated with a BMR of 5%
$BMDL_{10}$	BMDCL associated with a BMR of 10%
BMR	benchmark response
BSC	Board of Scientific Counselors
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act

DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure

LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NPN	blood nonprotein nitrogen
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA

OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture

USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D

OVERVIEW OF BASIC RADIATION PHYSICS, CHEMISTRY, AND BIOLOGY

Understanding the basic concepts in radiation physics, chemistry, and biology is important to the evaluation and interpretation of radiation-induced adverse health effects and to the derivation of radiation protection principles. This appendix presents a brief overview of the areas of radiation physics, chemistry, and biology and is based to a large extent on the reviews of Mettler and Moseley (1985), Hobbs and McClellan (1986), Eichholz (1982), Hendee (1973), Cember (1996, 2009), and Early et al. (1979).

D.1 RADIONUCLIDES AND RADIOACTIVITY

The substances we call elements are composed of atoms. Atoms in turn are made up of neutrons, protons and electrons: neutrons and protons in the nucleus and electrons in a cloud of orbits around the nucleus. Nuclide is the general term referring to any nucleus along with its orbital electrons. The nuclide is characterized by the composition of its nucleus and hence by the number of protons and neutrons in the nucleus. All atoms of an element have the same number of protons (this is given by the atomic number) but may have different numbers of neutrons (this is reflected by the atomic mass numbers or atomic weight of the element). Atoms with different atomic mass but the same atomic numbers are referred to as isotopes of an element.

The numerical combination of protons and neutrons in most nuclides is such that the nucleus is quantum mechanically stable and the atom is said to be stable, i.e., not radioactive; however, if there are too few or too many neutrons, the nucleus is unstable and the atom is said to be radioactive. Unstable nuclides undergo radioactive transformation, a process in which a neutron or proton converts into the other and a beta particle is emitted, or else an alpha particle is emitted. Each type of decay is typically accompanied by the emission of gamma rays. These unstable atoms are called radionuclides; their emissions are called ionizing radiation; and the whole property is called radioactivity. Transformation or decay results in the formation of new nuclides some of which may themselves be radionuclides, while others are stable nuclides. This series of transformations is called the decay chain of the radionuclide. The first radionuclide in the chain is called the parent; the subsequent products of the transformation are called progeny, daughters, or decay products.

In general there are two classifications of radioactivity and radionuclides: natural and artificial (man-made). Naturally-occurring radioactive material (NORM) exists in nature and no additional energy is necessary to place them in an unstable state. Natural radioactivity is the property of some naturally occurring, usually heavy elements, that are heavier than lead. Radionuclides, such as radium and uranium, primarily emit alpha particles. Some lighter elements such as carbon-14 and tritium (hydrogen-3) primarily emit beta particles as they transform to a more stable atom. Natural radioactive atoms heavier than lead cannot attain a stable nucleus heavier than lead. Everyone is exposed to background radiation from naturally-occurring radionuclides throughout life. This background radiation is the major source of radiation exposure to man and arises from several sources. The natural background exposures are frequently used as a standard of comparison for exposures to various artificial sources of ionizing radiation.

Artificial radioactive atoms are produced either as a by-product of fission of uranium or plutonium atoms in a nuclear reactor or by bombarding atoms with particles (such as neutrons, protons, or heavy nuclei) at high velocity via a particle accelerator. Goals of these efforts can include producing medical isotopes or new elements. These artificially produced radioactive elements usually decay by emission of particles, such as alpha particles, positive or negative beta particles, and one or more high energy photons (gamma rays). Unstable (radioactive) atoms of any element can be produced.

Both naturally occurring and artificial radioisotopes find application in medicine, industrial products, and consumer products. Some specific radioisotopes, called fall-out, are still found in the environment as a result of nuclear weapons use or testing, or nuclear power plant accidents (e.g., Three Mile Island Unit 2, Chernobyl, and Fukushima Dai-ichi).

D.2 RADIOACTIVE DECAY

D.2.1 Principles of Radioactive Decay

The stability of an atom is the result of the balance of the forces of the various components of the nucleus. An atom that is unstable (a radionuclide) will release energy (decay) in various ways and transform to stable atoms or to intermediate radioactive species called progeny or daughters, often with the release of ionizing radiation. If there are either too many or too few neutrons for a given number of protons, the resulting nucleus may undergo transformation. For some elements, a chain of progeny decay products may be produced until stable atoms are formed. Radionuclides can be characterized by the type and energy of the radiation emitted, the rate of decay, and the mode of decay. The mode of decay indicates how a parent compound undergoes transformation. Radiations considered here are primarily of nuclear origin, i.e., they arise from nuclear excitation, usually caused by the capture of charged or uncharged nucleons by a nucleus, or by the radioactive decay or transformation of an unstable nuclide. The type of radiation may be categorized as charged or uncharged particles, protons, and fission products) or electromagnetic radiation (gamma rays and x rays). Table D-1 summarizes the basic characteristics of the more common types of radiation encountered.

D.2.2 Half-Life and Activity

For any given radionuclide, the rate of decay is a first-order process that is constant, regardless of the radioactive atoms present and is characteristic for each radionuclide. The process of decay is a series of random events; temperature, pressure, or chemical combinations do not affect the rate of decay. While it may not be possible to predict exactly which atom is going to undergo transformation at any given time, it is possible to predict, on average, the fraction of the radioactive atoms that will transform during any interval of time.

The *activity* is a measure of the quantity of radioactive material. For these radioactive materials it is customary to describe the activity as the number of disintegrations (transformations) per unit time. The unit of activity is the curie (Ci), which was originally related to the activity of one gram of radium, but is now defined as the disintegration or transformation rate occurring in a quantity of radioactive material. The definition is:

1 curie (Ci) $= 3.7 \times 10^{10}$ disintegrations (transformations)/second (dps) or
$= 2.22 \times 10^{12}$ disintegrations (transformations)/minute (dpm).

The SI unit of activity is the becquerel (Bq); 1 Bq = that quantity of radioactive material in which there is 1 transformation/second. Since activity is proportional to the number of atoms of the radioactive material, the quantity of any radioactive material is usually expressed in curies, regardless of its purity or concentration. The transformation of radioactive nuclei is a random process, and the number of transformations is directly proportional to the number of radioactive atoms present. For any pure radioactive substance, the rate of decay is usually described by its radiological half-life, $t_{½}$, i.e., the time it takes for a specified source material to decay to half its initial activity. The specific activity is an indirect measure of the rate of decay, and is defined as the activity per unit mass or per unit volume. The higher the specific activity of a radioisotope, the faster it is decaying.

The activity of a radionuclide at time t may be calculated by:

$$A = A_o e^{-0.693t/t_{½}},$$

where A = the activity in dps or curies or becquerels,
A_o = the activity at time zero,
t = the time at which measured, and
$t_{½}$ = the radiological half-life of the radionuclide ($t_{½}$ and t must be in the same units of time).

The time when the activity of a sample of radioactivity becomes one-half its original value is the radioactive half-life and is expressed in any suitable unit of time.

APPENDIX D

Table D-1. Characteristics of Nuclear Radiations

Radiation	Rest mass[a]	Charge	Typical energy range	Path length[b]		Comments
				Air	Solid	
Alpha (α)	4.00 amu	+2	4–10 MeV	5–10 cm	25–80 μm	Identical to ionized He nucleus
Negatron (β^-)	5.48×10^{-4} amu; 0.51 MeV	–1	0–4 MeV	0–10 m	0–1 cm	Identical to electron
Positron (β^+)	5.48×10^{-4} amu; 0.51 MeV	+1	0-4 MeV	0–10 m	0–1 cm	Identical to electron except for sign of charge
Neutron	1.00866 amu; 939.565 MeV	0	0–15 MeV	b	b	Half life: 10.183 min
X ray (e.m. photon)	–	0	5 keV–100 keV	b	b	Photon from transition of an electron between atomic orbits
Gamma (γ) (e.m. photon)	–	0	10 keV–3 MeV	b	b	Photon from nuclear transformation

[a] The rest mass (in amu) has an energy equivalent in MeV that is obtained using the equation $E=mc^2$, where 1 amu = 932 MeV.
[b] Path lengths are not applicable to x- and gamma rays since their intensities decrease exponentially; path lengths in solid tissue are variable, depending on particle energy, electron density of material, and other factors.

amu = atomic mass unit; e.m. = electromagnetic; MeV = MegaElectron Volts

The specific activity is a measure of activity, and is defined as the activity per unit mass or per unit volume. This activity is usually expressed in curies per gram and may be calculated by

$$\text{curies/gram} = 1.3 \times 10^8 / (t_{½}) \text{ (atomic weight)} \quad \text{or}$$

$$[3.577 \times 10^5 \times \text{mass(g)}] / [t_{½} \times \text{atomic weight}]$$

where $t_{½}$ = the radiological half-life in days.

In the case of radioactive materials contained in living organisms, an additional consideration is made for the reduction in observed activity due to regular processes of elimination of the respective chemical or biochemical substance from the organism. This introduces a rate constant called the biological half-life (t_b) which is the time required for biological processes to eliminate one-half of the activity. This time is virtually the same for both stable and radioactive isotopes of any given element.

Under such conditions the time required for a radioactive element to be halved as a result of the combined action of radioactive decay and biological elimination is the effective clearance half-time:

$$t_{eff} = (t_b \times t_{½}) / (t_b + t_{½}).$$

Table D-2 presents representative effective half-lives of particular interest.

Table D-2. Half-Lives of Some Radionuclides in Adult Body Organs

		Half-life[a]		
Radionuclide	Critical organ	Physical	Biological	Effective
Uranium 238	Kidney	4,460,000,000 y	4 d	4 d
Hydrogen 3[b] (Tritium)	Whole body	12.3 y	10 d	10 d
Iodine 131	Thyroid	8 d	80 d	7.3 d
Strontium 90	Bone	28 y	50 y	18 y
Plutonium 239	Bone surface	24,400 y	50 y	50 y
	Lung	24,400 y	500 d	500 d
Cobalt 60	Whole body	5.3 y	99.5 d	95 d
Iron 55	Spleen	2.7 y	600 d	388 d
Iron 59	Spleen	45.1 d	600 d	42 d
Manganese 54	Liver	303 d	25 d	23 d
Cesium 137	Whole body	30 y	70 d	70 d

[a]d = days, y = years
[b]Mixed in body water as tritiated water

D.2.3 Interaction of Radiation with Matter

Both ionizing and nonionizing radiation will interact with materials; that is, radiation will lose kinetic energy to any solid, liquid or gas through which it passes by a variety of mechanisms. The transfer of energy to a medium by either electromagnetic or particulate radiation may be sufficient to cause formation of ions. This process is called ionization. Compared to other types of radiation that may be absorbed, such as radio waves or microwave radiation, ionizing radiation deposits a relatively large amount of energy into a small volume.

The method by which incident radiation interacts with the medium to cause ionization may be direct or indirect. Electromagnetic radiations (x rays and gamma photons) and neutral particles (neutrons) are indirectly ionizing; that is, they give up their energy in various interactions with cellular molecules, and the energy is then utilized to produce a fast-moving charged particle such as an electron. It is the electron that then may react with and transfer energy to a target molecule. This particle is called a “primary ionizing particle. Charged particles, in contrast, strike the tissue or medium and directly react with target molecules, such as oxygen or water. These particulate radiations are directly ionizing radiations. Examples of directly ionizing particles include alpha and beta particles. Indirectly ionizing radiations are always more penetrating than directly ionizing particulate radiations.

Mass, charge, and velocity of a particle, as well as the electron density of the material with which it interacts, all affect the rate at which ionization occurs. The higher the charge of the particle and the lower the velocity, the greater the propensity to cause ionization. Heavy, highly charged particles, such as alpha particles, lose energy rapidly with distance and, therefore, do not penetrate deeply. The result of these interaction processes is a gradual slowing down of any incident particle until it is brought to rest or "stopped" at the end of its range.

D.2.4 Characteristics of Emitted Radiation

D.2.4.1 Alpha Emission. In alpha emission, an alpha particle consisting of two protons and two neutrons is emitted with a resulting decrease in the atomic mass number by four and reduction of the atomic number of two, thereby changing the parent to a different element. The alpha particle is identical to a helium nucleus consisting of two neutrons and two protons. It results from the radioactive decay of some heavy elements such as uranium, plutonium, radium, thorium, and radon. All alpha particles emitted by a given radioisotope have the same energy.

Most of the alpha particles that are likely to be found have energies in the range of about 4 to 8 MeV, depending on the isotope from which they came.

The alpha particle has an electrical charge of +2. Because of this double positive charge and their size, alpha particles have great ionizing power and, thus, lose their kinetic energy quickly. This results in very little penetrating power. In fact, an alpha particle cannot penetrate a sheet of paper. The range of an alpha particle (the distance the charged particle travels from the point of origin to its resting point) is about 4 cm in air, which decreases considerably to a few micrometers in tissue. These properties cause alpha emitters to be hazardous only if there is internal contamination (i.e., if the radionuclide is inside the body).

D.2.4.2 Beta Emission. A beta particle (β) is a high-velocity electron ejected from a disintegrating nucleus. The particle may be either a negatively charged electron, termed a negatron (β^{Z}) or a positively charged electron, termed a positron (β^{E}). Although the precise definition of "beta emission" refers to both β^{Z} and β^{E}, common usage of the term generally applies only to the negative particle, as distinguished from the positron emission, which refers to the β^{E} particle.

D.2.4.2.1 Beta Negative Emission. Beta particle (β^{Z}) emission is another process by which a radionuclide, with a neutron excess achieves stability. Beta particle emission decreases the number of neutrons by one and increases the number of protons by one, while the atomic mass number remains unchanged.4 This transformation results in the formation of a different element. The energy spectrum of beta particle emission ranges from a certain maximum down to zero with the mean energy of the spectrum being about one-third of the maximum. The range in tissue is much less. Beta negative emitting radionuclides can cause injury to the skin and superficial body tissues, but mostly present an internal contamination hazard.

D.2.4.2.2 Positron Emission. In cases in which there are too many protons in the nucleus, positron emission may occur. In this case a proton may be thought of as being converted into a neutron, and a positron (β^{E}) is emitted.[1] This increases the number of neutrons by one, decreases the number of protons by one, and again leaves the atomic mass number unchanged. The gamma radiation resulting from the annihilation (see glossary) of the positron makes all positron emitting isotopes more of an external radiation hazard than pure β emitters of equal energy.

D.2.4.2.3 Gamma Emission. Radioactive decay by alpha, beta, or positron emission, or electron capture often leaves some of the energy resulting from these changes in the nucleus. As a result, the nucleus is raised to an excited level. None of these excited nuclei can remain in this high-energy state. Nuclei release this energy returning to ground state or to the lowest possible stable energy level. The energy released is in the form of gamma radiation (high energy photons) and has an energy equal to the change in the energy state of the nucleus. Gamma and x rays behave similarly but differ in their origin; gamma emissions originate in the nucleus while x rays originate in the orbital electron structure or from rapidly changing the velocity of an electron (e.g., as occurs when shielding high energy beta particles or stopping the electron beam in an x ray tube).

D.3 ESTIMATION OF ENERGY DEPOSITION IN HUMAN TISSUES

Two forms of potential radiation exposures can result: internal and external. The term exposure denotes physical interaction of the radiation emitted from the radioactive material with cells and tissues of the human body. An exposure can be "acute" or "chronic" depending on how long an individual or organ is exposed to the radiation. Internal exposures occur when radionuclides, which have entered the body (e.g., through the inhalation, ingestion, or dermal pathways), undergo radioactive decay resulting in the deposition of energy to internal organs. External exposures occur when radiation enters the body directly from sources located outside the body, such as radiation emitters from radionuclides on ground surfaces, dissolved in water, or dispersed in the air. In general, external exposures are from material emitting gamma radiation, which readily penetrate the skin and internal organs. Beta and alpha radiation from external sources are far less penetrating and deposit their energy primarily on the skin's outer layer. Consequently, their contribution to the absorbed dose of the total body dose, compared to that deposited by gamma rays, may be negligible.

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4 Neutrinos accompany negative beta particle emissions; anti-neutrinos accompany positron emissions

Characterizing the radiation dose to persons as a result of exposure to radiation is a complex issue. It is difficult to: (1) measure internally the amount of energy actually transferred to an organic material and to correlate any observed effects with this energy deposition; and (2) account for and predict secondary processes, such as collision effects or biologically triggered effects, that are an indirect consequence of the primary interaction event. Radiation exposure (a measure of ionization density in air) is sometimes used as a surrogate for radiation dose in tissue from external radiation. Both exposure and dose are described below.

D.3.1 Exposure (Roentgen). The roentgen (R) is a unit of x or gamma-ray exposure and is a measured by the amount of ionization caused in air by gamma or x radiation. One roentgen produces 2.58×10^{-4} coulomb per kilogram of air. In the case of gamma radiation, over the commonly encountered range of photon energy, the energy deposition in tissue for an exposure of 1 R is about 0.0096 joules (J)/kg of tissue. Exposure is only defined for x and gamma radiation ionization in air, and is often incorrectly interchanged with the term dose.

D.3.2 Absorbed Dose (Gy, rad) and Absorbed Dose Rate (Gy/hr, rad/hr). The absorbed dose is defined as the energy absorbed from the incident radiation by a unit mass of the tissue or organ (dm). The differential equation for absorbed dose is:

$$D = de/dm$$

where: D = absorbed dose
e = mean energy deposited
m = mass in which the energy was deposited.

The SI unit of absorbed dose in any medium is the J/kg with the special name of Gray (Gy), where 1 J/kg = 10,000 ergs/gram = 1 Gy. In the historical system, 0.01 J/kg = 100 ergs/g = 1 rad, so 1 Gy = 100 rad.. For neutrons, the absorbed dose may be estimated using the similar metric, kinetic energy released in matter (kerma). Kerma is the sum of initial kinetic energies of all charged ionizing particles liberated in a unit mass.

Absorbed dose is a measurable quantity, so there are primary national and international standards for its determination. In practice, absorbed dose is averaged over organ or tissue volumes. This allows the absorbed dose from both external and internal sources of radiation to be added. For low doses, the acceptance of the linear no threshold (LNT) theory allows the correlation of dose with degree of adverse deterministic health effects. Radiation that does not penetrate tissue well (low energy x-rays, beta particles, and alpha particles) can produce a nonuniform distribution of absorbed dose resulting in differential health effects across an organ or tissue. An example is using shielding in radiation therapy so that a kidney tumor receives a lethal dose while sparing as much health tissue as practical, thus maximizing the remaining kidney function.

Internal and external absorbed doses delivered by radiation sources are not usually instantaneous but are distributed over extended periods of time. The resulting rate of change of the absorbed dose to a small volume of mass is referred to as the absorbed dose rate, which has units of Gy/unit time or rad/unit time.

As a rough conversion, an exposure of 1 R in air results in an absorbed dose to soft tissue of approximately 0.01 J/kg.

See text below on other units of measure.

D.4 UNITS IN RADIATION PROTECTION AND REGULATION

D.4.1 Equivalent Dose (or Dose Equivalent)

Equivalent dose (international term) and dose equivalent (US term)are a radiation protection quantity used for setting limits that help ensure that deterministic effects (e.g. damage to a particular tissue) are kept within acceptable levels. The SI unit of equivalent dose is the J/kg, has the special name of Sievert (Sv) or rem, and is abbreviated H_T. It is a special radiation protection quantity that is used, for administrative and radiation safety purposes only, to

express the absorbed dose in a manner which considers the difference in biological effectiveness of various kinds of ionizing radiation. The equivalent dose concept is applicable only to doses that are not great enough to produce biomedical effects.

The equivalent dose in an organ or tissue (H_T) is determined by multiplying the absorbed dose by a radiation weighting factor and any modifying factors at the location of interest. The absorbed dose in an organ or tissue from radiation of type R ($D_{T,R}$) is a measurable or estimable quantity, while the radiation weighting factor (ω_R) for each primary radiation type (ω_R) has been studied and recommendations made for their values. The formula for calculating equivalent dose is:

$$H_T = \sum_R \omega_R D_{T,R}, \text{ or } \sum_R Q_R D_{T,R}.$$

Where ω_R = radiation weighting factor,
$D_{T,R}$ = absorbed dose to tissue T from radiation type R, and
Q_R = quality factor.

The radiation weighting factor (ω) or quality factor (Q) is a dimensionless quantity that depends in part on the stopping power for charged particles, and it accounts for the differences in biological effectiveness found among the types of radiation. Originally, relative biological effectiveness (RBE) was used rather than ω or Q to define the quantity, rem, which is of use in risk assessment. The NRC and DOE in the US, and the ICRU and ICRP in most of the remaining international community havepublished values for quality factors and radiation weighting factors provided in Tables D-3 and D-4.

The equivalent dose rate (or dose equivalent rate in the US) is the time rate of change of the equivalent dose (or dose equivalent) to organs and tissues and is expressed as Sv/unit time (or rem/unit time).

Table D-3. Recommended Values of Quality Factors and Radiation Weighting Factors

Type of Radiation	Quality Factor (NRC 2011)	Radiation Weighting Factor (w_R) (ICRP 2007)
Photons (x and γ rays)	1	1
Electrons	1	
Electrons and muons		1
High energy protons	10	
Protons and charged pions		2
Alpha particles, multiple-charged particles, fission fragments and heavy particles of unknown charge	20	
Alpha particles, fission fragments, heavy ions		20
Neutrons of unknown energy	10	
Neutrons of known energy	See Table D-4	A continuous function of neutron energy (range 2.4-21; see equation)

Source:
USNRC. 2011. Standards for the protection against radiation, tables 1004(b).1 and 1004(b).2. 10 CFR 20.1004. U.S. Nuclear Regulatory Commission, Washington, D.C.
ICRP
Radiation weighting factors for neutrons are based on particle energy according to the following formulas (ICRP 2007):

$$\omega_R = \begin{cases} 2.5 + 18.2e^{-\frac{\ln(E_n^2)}{6}}, & E_n < 1\ \text{MeV} \\ 5.0 + 17.0e^{-\frac{\ln(2E_n^2)}{6}}, & 1\ MeV \leq E_n \leq 50\ \text{MeV} \\ 2.5 + 3.25e^{-\frac{\ln(0.04E_n^2)}{6}}, & E_n > 50\ \text{MeV} \end{cases}$$

Table D-4 Mean Quality Factors, Q, and Fluence per Unit Dose Equivalent for Monoenergetic Neutrons

	Neutron energy (MeV)	Quality factor[a](Q)	Fluence per unit dose equivalent[b](neutrons $cm^{-2}rem^{-1}$)
(thermal)	2.5×10^{-8}	2	980×10^{6}
	1×10^{-7}	2	980×10^{6}
	1×10^{-6}	2	810×10^{6}
	1×10^{-5}	2	810×10^{6}
	1×10^{-4}	2	840×10^{6}
	1×10^{-3}	2	980×10^{6}
	1×10^{-2}	2.5	1010×10^{6}
	1×10^{-1}	7.5	170×10^{6}
	5×10^{-1}	11	39×10^{6}
	1	11	27×10^{6}
	2.5	9	29×10^{6}
	5	8	23×10^{6}
	7	7	24×10^{6}
	10	6.5	24×10^{6}
	14	7.5	17×10^{6}
	20	8	16×10^{6}
	40	7	14×10^{6}
	60	5.5	16×10^{6}
	1×10^{2}	4	20×10^{6}

	2×10^2	3.5	19×10^6
	3×10^2	3.5	16×10^6
	4×10^2	3.5	14×10^6

D.4.2 Relative Biological Effectiveness

RBE is used to denote the experimentally determined ratio of the absorbed dose from one radiation type to the absorbed dose of a reference radiation required to produce an identical biological effect under the same conditions. Gamma rays from cobalt-60, cesium-137, and 200–250 keV x-rays have been used as reference standards. The term RBE has been widely used in experimental radiobiology, and the term radiation weighting factor used in calculations of dose equivalent for radiation safety purposes (ICRP 2007; NCRP 1971; UNSCEAR 1982). RBE applies only to a specific biological end point, in a specific exposure, under specific conditions to a specific species. There are no generally accepted values of RBE.

D.4.3 Effective Dose or Effective Dose Equivalent

In an attempt to compare stochastic (e.g., cancer) detriment from absorbed dose of radiation in a limited portion of the body with the detriment from total body dose, the ICRP (1977) derived a concept of effective dose equivalent. ICRP changed this term to effective dose in 1990 (ICRP 1990) and reintroduced the term "effective dose equivalent" in 2007 (ICRP 2007). The term "effective dose equivalent" allows for the addition or direct comparison of cancer and genetic risk from various partial or whole body doses. In the U.S., the term "effective dose equivalent" is presently used by the NRC (NRC 2011) and DOE.

The effective dose (or effective dose equivalent) approach was developed to overcome limitations in using absorbed dose as a metric of the stochastic impact of ionizing radiation. The absorbed dose is usually defined as the mean absorbed dose within an organ or tissue. This represents a simplification of the actual problem. Normally when an individual ingests or inhales a radionuclide or is exposed to external radiation that enters the body (gamma), the dose is not uniform throughout the whole body.

The simplifying assumption is that the detriment will be the same whether the body is uniformly or non-uniformly irradiated. This required the development of a tissue weighting factor, which represents the estimated proportion of the stochastic risk resulting from tissue, T, to the stochastic risk when the whole body is uniformly irradiated for occupational exposures under certain conditions (ICRP 1977).

The effective dose (or effective dose equivalent) (H_E) is weighted for both the type of radiation (R) and the type of tissue (T), and has the formula:

$$H_E = \sum_T \omega_T H_T = \sum_T \omega_T \sum_R \omega_R D_{T,R},$$

where H_E = the effective dose (or effective dose equivalent) in tissue T,
ω_T = the tissue weighting factor in tissue T,
H_T = the equivalent dose (or dose equivalent dose),
ω_R = the radiation weighting factor, and
$D_{T,R}$ = the absorbed dose from radiation R to tissue T.

Tissue weighting factors for selected tissues are listed in Table D-5.

Table D-5. Tissue Weighting Factors for Calculating Effective Dose (or Effective Dose Equivalent) for Selected Tissues

Tissue	Tissue Weighting factor		
	NRC (2011) /ICRP26	NCRP115 and ICRP60	ICRP103
Bladder		0.05	0.04
Bone marrow (red)	0.12	0.12	0.12
Bone surface	0.03	0.01	0.01
Brain			0.01
Breast	0.15	0.05	0.12
Colon	–	0.12	0.12
Esophagus	–	0.05	0.04
Gonads	0.25	0.20	0.08
Liver	–	0.05	0.04
Lung	0.12	0.12	0.12
Salivary glands			0.01
Skin	–	0.01	0.01
Stomach	–	0.12	0.12
Thyroid	0.03	0.05	0.04
Subtotal	0.70	0.95	0.88
Remainder	0.30	0.05	0.12[a]
Total	1.00	1.00	1.00

ICRP60 = International Commission on Radiological Protection, 1990 Recommendations of the ICRP
NCRP115 = National Council on Radiation Protection and Measurements. 1993. Risk Estimates for Radiation Protection, Report 115. Bethesda, Maryland
NRC = Nuclear Regulatory Commission, Title 10, Code of Federal Regulations, Part 20
[a]ICRP Publication 103 remainder tissues include adrenals, extrathoracic (ET) region, gall bladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate, small intestine, spleen, thymus, uterus/cervix

The ICRU (1980), ICRP (1984), and NCRP (1985) recommended that the terms rad, roentgen, curie, and rem be replaced by the SI units: gray (Gy), Coulomb per kilogram (C/kg), Becquerel (Bq), and sievert (Sv), respectively. The relationship between the historical units and the international system of units (SI) for radiological quantities is shown in Table D-6.

Table D-6. Comparison of Common and SI Units for Radiation Quantities

Quantity (Abbreviation)	Historical Unit	Historical Definition	SI unit	SI Definition
Activity (A)	curie (Ci)	3.7×10^{10} transformations s^{-1}	becquerel (Bq)	s^{-1}
Absorbed dose (D)	rad (rad)	10^{-2} Jkg^{-1}	gray (Gy)	Jkg^{-1}
Absorbed dose rate ($\dot{D}$)	rad per second (rad s^{-1})	10^{-2} $Jkg^{-1}s^{-1}$	gray per second (Gy s^{-1})	Jkg^{-1} s^{-1}
Equivalent Dose (or Dose equivalent) (H_T)	rem	10^{-2} Jkg^{-1}	sievert (Sv)	Jkg^{-1}

Equivalent Dose Rate (or Dose equivalent rate)	rem per second (rem s^{-1})	10^{-2} $Jkg^{-1}s^{-1}$	sievert per second (Sv s^{-1})	Jkg^{-1} s^{-1}
Effective dose (or Effective Dose Equivalent) (H_E)	rem	10^{-2} Jkg^{-1}	sievert (Sv)	Jkg^{-1}
Linear energy transfer (LET)	kiloelectron volts per micrometer (keV μm^{-1})	$1.602x10^{-10}$ Jm^{-1}	kiloelectron volts per micrometer (keV μm^{-1})	$1.602x10^{-10}$ Jm^{-1}

Jkg^{-1} = Joules per kilogram; $Jkg^{-1}s^{-1}$ = Joules per kilogram per second; Jm^{-1} = Joules per meter; s^{-1} = per second

D.4.4 Working Levels and Working Level Months (for Radon Dosimetry). Working level (WL) is a measure of the atmospheric concentration of radon and its short-lived progeny. One WL is defined as any combination of short-lived radon progeny (through polonium-214 [^{214}Po]), per liter of air, that will result in the emission of $1.3x10^5$ MeV of alpha energy. An activity concentration of 100 pCi ^{222}Rn/L of air, in equilibrium with its progeny, corresponds approximately to a potential alpha-energy concentration of 1 WL. The WL unit can also be used for thoron or ^{220}Rn. In this case, $1.3x10^5$ MeV of alpha energy (1 WL) is released by 7.5 pCi ^{220}Rn/L in equilibrium with its progeny. The potential alpha energy exposure of miners is commonly expressed in the unit Working Level Month (WLM). One WLM corresponds to inhalinga concentration of 1 WL for the reference period of 170 hours, or more generally

WLM = concentration (WL) x exposure time (months) / (one “month” = 170 working hours).

D.5 Dosimetry Models

Dosimetry models are used to estimate the dose from internally deposited radioactive substances. The models for internal dosimetry consider the amount of radionuclides entering the body, the factors affecting their movement or transport through the body, distribution and retention of radionuclides in the body, and the energy deposited in organs and tissues from the radiation that is emitted during spontaneous decay processes. The dose pattern for radioactive materials in the body may be strongly influenced by the route of entry of the material. For industrial workers, inhalation of radioactive particles with pulmonary deposition and puncture wounds with subcutaneous deposition have been the most frequent. The general population has been exposed via ingestion, inhalation, and external exposure to low levels of naturally occurring radionuclides as well as artificial radionuclides used in nuclear medicine procedures and released from isotope generation facilities, nuclear weapons testing, and nuclear reactor operations and accidents.

The models for external dosimetry consider only the photon doses (and neutron doses, where applicable) to organs of individuals who are immersed in air or are exposed to a contaminated object.

D.5.1 Ingestion. Ingestion of radioactive materials is most likely to occur from eating food or drinking water containing naturally occurring radioactive material and possibly also contaminated with artificial radionuclides. Also, a portion of inhaled radionuclides initially deposited in the lung will relocate to the throat and be swallowed. Ingestion of a sufficient amount of radioactive material may result in toxic effects as a result of either absorption of the radionuclide or irradiation of the gastrointestinal tract during passage through the tract, or a combination of both. The fraction of a radioactive material absorbed from the gastrointestinal tract is variable, depending on the specific element, the physical and chemical form of the material ingested, and the diet, as well as some other metabolic and physiological factors. The absorption of some elements is influenced by age, usually with higher absorption in the very young.

D.5.2 Inhalation. The nose and mouth have long been recognized as being a major portal of entry for both nonradioactive and radioactive materials. The deposition of particles within the lung is largely dependent upon the size and shape of the particles being inhaled (sometimes termed the atmospheric mean aerodynamic diameter or AMAD). After a particle is deposited, its retention will depend upon the physical and chemical properties of the dust and the physiological status of the lung. The retention of the particle in the lung depends on the location of

deposition, in addition to the physical and chemical properties of the particles. The converse of pulmonary retention is pulmonary clearance. There are three distinct mechanisms of clearance which operate simultaneously. Ciliary clearance acts only in the upper respiratory tract. The second and third mechanisms act mainly in the deep respiratory tract. These are phagocytosis and absorption. Phagocytosis is the engulfing of foreign bodies by alveolar macrophages and their subsequent removal either up the ciliary "escalator" or by entrance into the lymphatic system. Some inhaled soluble particles are absorbed into the blood and translocated to other organs and tissues.

D.5.3 Internal Emitters

An internal emitter is a radionuclide that is inside the body. The absorbed dose from internally deposited radioisotopes depends on the energy absorbed per unit tissue by the irradiated tissue. For a radioisotope distributed uniformly throughout an infinitely large medium, the concentration of absorbed energy must be equal to the concentration of energy emitted by the isotope. An infinitely large medium may be approximated by a tissue mass whose dimensions exceed the range of the particle. All alpha and most beta radiation will be absorbed in the organ (or tissue) of reference. Gamma-emitting isotope emissions are penetrating radiation, and a substantial fraction of gamma energy may not be absorbed in tissue. The dose to an organ or tissue is a function of the effective retention half-time, the energy released in the tissue, the amount of radioactivity initially introduced, and the mass of the organ or tissue.

D.6 BIOLOGICAL EFFECTS OF RADIATION

When biological material is exposed to ionizing radiation, a chain of cellular events occurs as the ionizing particle passes through the biological material. A number of theories have been proposed to describe the interaction of radiation with biologically important molecules in cells and to explain the resulting damage to biological systems from those interactions. Many factors may modify the response of a living organism to a given dose of radiation. Factors related to the exposure include the dose rate, the energy of the radiation, and the temporal pattern of the exposure (e.g., protracted or fractionated exposures). Biological considerations include factors such as species, age, sex, and the portion of the body exposed. Several excellent reviews of the biological effects of radiation have been published, and the reader is referred to these for a more in-depth discussion (Brodsky 1996; Klaassen 2001; Hobbs and McClellan 1986; ICRP 1984; Mettler and Moseley 1985; Rubin and Casarett 1968).

D.6.1 Radiation Effects at the Cellular Level

According to Mettler and Moseley (1985), at acute doses up to 10 rad (100 mGy), single strand breaks in DNA may be produced. These single strand breaks may be repaired rapidly. With doses in the range of 0.5-5 Gy (50–500 rad), irreparable double-stranded DNA breaks are likely, resulting in cellular reproductive death after one or more divisions of the irradiated parent cell. At large doses of radiation, usually greater than 5 Gy (500 rad), direct cell death before division (interphase death) may occur from the direct interaction of free-radicals with essentially cellular macromolecules. Morphological changes at the cellular level, the severity of which are dose-dependent, may also be observed.

The sensitivity of various cell types varies. According to the Bergonie-Tribondeau law, the sensitivity of cell lines is directly proportional to their mitotic rate and inversely proportional to the degree of differentiation (Mettler and Moseley 1985). Rubin and Casarett (1968) devised a classification system that categorized cells according to type, function, and mitotic activity. The categories range from the most sensitive type, "vegetative intermitotic cells," found in the stem cells of the bone marrow and the gastrointestinal tract, to the least sensitive cell type, "fixed postmitotic cells," found in striated muscles or long-lived neural tissues.

Cellular changes may result in cell death, which if extensive, may produce irreversible damage to an organ or tissue or may result in the death of the individual. If the cell recovers, altered metabolism and function may still occur, which may be repaired or may result in the manifestation of clinical symptoms. These changes may also be expressed at a later time as tumors, cellular mutations, or transformed tissue (scar tissue) which may result in abnormal tissue or compromised function.

D.6.2 Radiation Effects at the Organ Level

In most organs and tissues the injury and the underlying mechanism for that injury are complex and may involve a combination of events. The extent and severity of this tissue injury are dependent upon the radiosensitivity of the various cell types in that organ system. Rubin and Casarett (1968) describe and schematically display the events following radiation in several organ system types. These include: a rapid renewal system, such as the gastrointestinal mucosa; a slow renewal system, such as the pulmonary epithelium; and a nonrenewal system, such as neural or muscle tissue. In the rapid renewal system, organ injury results from the direct destruction of highly radiosensitive cells, such as the stem cells in the bone marrow. Injury may also result from constriction of the microcirculation and from edema and inflammation of the basement membrane, designated as the histohematic barrier (HHB), which may progress to fibrosis. In slow renewal and nonrenewal systems, the radiation may have little effect on the parenchymal cells, but ultimate parenchymal atrophy and death over several months result from HHB fibrosis and occlusion of the microcirculation.

D.6.3 Low Level Radiation Effects

Cancer is the major latent harmful effect produced by ionizing radiation and the one that most people exposed to radiation are concerned about. The ability of alpha, beta, and gamma radiation to produce cancer in virtually every tissue and organ in laboratory animals has been well-demonstrated, while radiogenic cancer has not been observed in some human tissues and organs. The development of cancer is not an immediate effect. In humans, radiation-induced leukemia has the shortest latent period at 2 years, thyroid cancer after Chernobyl showed up in children about four years after the accident, while other radiation induced cancers have latent periods >20 years. For the non-radiogenic cancers, it has been hypothesized either that repair mechanisms effectively protect the individual or that the latency period exceeds the current human life span (Raabe 2010). The mechanism by which cancer is induced in living cells is complex and is a topic of intense study. Exposure to ionizing radiation can produce cancer; however, some sites appear to be more common than others, such as the breast, lung, stomach, and thyroid.

DNA is a major target molecule during exposure to ionizing radiation. Other macromolecules, such as lipids and proteins, are also at risk of damage when exposed to ionizing radiation. The genotoxicity of ionizing radiation is an area of intense study, as damage to the DNA is ultimately responsible for many of the adverse toxicological effects ascribed to ionizing radiation, including cancer. Damage to genetic material is basic to developmental or teratogenic effects, as well.

There is limited evidence of non-cancer human effects at low radiation doses. Non-cancer effects that have been reported are associated with the Japanese atomic bomb survivor population and include neurological and cardiovascular effects. Neurological effects were observed in fetuses exposed to prompt radiation during the detonations while they were in gestation weeks 8–15, less so for weeks 16–25, and were not observed for other developmental time frames. Cardiovascular effects have been reported for atomic bomb survivors following 60 years of follow-up. These include a statistically significant increase in heart disease (% elevated relative risk per Gy with 95% confidence interval = 14 [6–23] %/Gy, $p<0.001$) and a non-statistically significant increase in stroke (9 [1–17]%/Gy, $p=0.02$) above a dose of 0.5 Gy. These radiation-induced circulatory effects may be increased by other factors such as smoking, microvascular damage in the kidney and associated hypertension, high serum cholerterol, diabetes, and infection.

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APPENDIX E. INDEX