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. They are below levels that might cause adverse health effects in the people most sensitive to such effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral, inhalation, and external 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 end point considered to be a 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.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide 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, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Uranium (Soluble Forms)
CAS number: Multiple
Date: July 2001
Profile status: Final
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Key to figure: 72
Species: Dog

MRL: $4x10^{-4}$ [ ] 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: (human study details or strain, number of animals per exposure/control group, sex, dose administration details):

Dogs (2–6 per group; sex and strain 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.) Dogs were bodily exposed to the dust. The activity median aerodynamic diameter (AMAD) for the particles is assumed to be 1.5–2.1 µm; average 1.8 µm (see Pozzani 1949). Clinical signs of toxicity, mortality, body weight changes, hematology, blood and urine chemistries were monitored. At the termination of the study, the animals were sacrificed and selected organs were histopathologically examined and uranium levels determined.

Effects noted in study and corresponding doses: Severe toxicity was observed at the highest concentration (9.2 mg U/m^3) leading to death. The 2 animals in this group showed signs of anorexia, rhinitis, and polydipsia. Later, these animals vomited blood, had severe weight loss and muscle weakness, and exhibited lassitude prior to death. Histopathological examination of the kidney revealed "severe" tubular lesions. Dogs exposed to 0.15 or 2.2 mg U/m^3 (6 per group) had no clinical signs of toxicity or significant weight changes. Clinical chemistry results included increased blood nonprotein nitrogen (NPN) with the maximum value over 200 mg/L in the 2 dogs exposed to 9.2 mg U/m^3. At 0.15 mg U/m^3, blood NPN and urinary amino acid nitrogen were normal in 3 dogs, while 1 of the 3 had increased urinary protein (not all tests were run on all dogs). Histopathological examination of the kidneys revealed "moderate" damage at 2.2 mg $U/m^3$and "slight" changes in 50% of the dogs at 0.15 mg U/m^3.

Dose endpoint used for MRL derivation:

[ ] NOAEL [x] LOAEL

0.15 mg/m^3; minimal microscopic lesions in the renal tubules in half the dogs examined. Proteinuria observed at 2.2 mg/m^3, severe renal damage at 9.2 mg/m^3.

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Uncertainty factors used in MRL derivation:

[ ] 1 [x] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [x] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

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

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
See calculations.

Was a conversion used from intermittent to continuous exposure?
Yes. See calculations.

Other additional studies or pertinent information that lend support to this MRL:
The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) has stated that limits for natural (and depleted) uranium in drinking water (the most important source of human exposure) should be based on the chemical toxicity rather than on a hypothetical radiological toxicity in skeletal tissues, which has not been observed in either man or animals (Wrenn et al. 1985).

Uranium is a nephrotoxin, exerting its toxic effect by chemical action mostly in the proximal tubule in humans and animals.

Numerous intermediate-duration uranium exposure studies in animals show that the most sensitive effect is renal toxicity (Dygert 1949a, 1949b, 1949c; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein 1949a, 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953). Dogs and rabbits appear to be the most sensitive species while rats are less sensitive. Susceptibility also depends on the chemical form of the uranium, the more water-soluble compounds being more toxic than the insoluble compounds. Nephrotoxic effects found in these animals range from minimal tubular lesions without functional effects to proteinuria, acute tubular necrosis, and renal failure.

Calculations

Since inhalation MRL's are derived for continuous exposure, the animal LOAEL derived from an intermittent exposure must be adjusted to continuous exposure:

For an exposure of 6 hours a day, 6 days a week,

$(0.15\ mg/m^3) * (6/24) * (6/7) = 0.032\ mg/m^3$ adjusted to continuous exposure.

The adjusted animal $NOAEL_{(ADJ)}$ must be converted to Human Equivalent Concentration ($LOAEL_{HEC}$) before applying uncertainty factors (UFs) adjustments (EPA 1994) for the derivation of the inhalation MRL:

$$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times RDDR$$

where:

$NOAEL_{[ADJ]}$ = duration adjusted laboratory animal NOAEL (in mg/m^3).
$NOAEL_{[HEC]}$ = human equivalent concentration of adjusted laboratory animal dose (in mg/m^3).
RDDR = Regional Deposited Dose Ratio

Since RDDR values are unavailable for dogs (EPA 1994), ATSDR used a default uncertainty factor of 3 for extrapolating from animals to humans as it incorporates the differences in physiology between dogs and humans. A default factor of 3 was used rather than the standard factor of 10 because of similarities in renal physiology between the two species, i.e., both acidify the urine by active transport of bicarbonate. Additional uncertainty factors of 3 for use of a minimal LOAEL and 10 for human intraspecies variability are used to calculate the intermediate-duration intermediate MRL.

$$Intermediate\ Inhalation\ MRL = \frac{NOAEL_{(HEC)}}{\prod UF\ Adjustments}$$

Therefore,

$$Intermediate\ Inhalation\ MRL = \frac{0.032\ mg/m^3}{90} = 4 \times 10^{-4}\ mg/m^3.$$

Agency Contact (Chemical Manager): Sam Keith.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Uranium (Insoluble Forms)
CAS number: Multiple
Date: July 2001
Profile status: Final
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Key to figure: 73
Species: Dog

MRL: $8x10^{-3}$ [ ] 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: (human study details or strain, number of animals per exposure/control group, sex, dose administration details):

Dogs (N=6–19; unspecified sex and strain) were exposed to uranium dioxide dust at concentrations of 1.1 mg U/m^3, 8.2 mg U/m^3, or 9.2 mg U/m^3 for 5 weeks, 6 days/weeks, 6 hours a 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 activity median aerodynamic diameter (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.

Effects noted in study and corresponding doses: No dogs died from exposure to uranium dioxide dust. Additionally, no significant weight changes, or biochemical changes in blood or urine were seen at any concentration. No hematological changes were attributable to uranium dioxide dust. Histopathological changes in the kidney were not observed in any group except for "very slight" renal tubular degeneration in 2 of 6 dogs at 8.2 mg U/m^3.

Dose endpoint used for MRL derivation:

[x] NOAEL [] LOAEL

1.1 mg/m^3; (LOAEL for minimal microscopic lesions in the renal tubules observed at 8.2 mg/m^3 in 2 of 6 dogs examined).

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [x] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

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

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
See calculations.

Was a conversion used from intermittent to continuous exposure?
Yes. See calculations.

Other additional studies or pertinent information that lend support to this MRL:
The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) has stated that limits for natural (and depleted) uranium in drinking water (the most important source of human exposure) should be based on the chemical toxicity rather than on a hypothetical radiological toxicity in skeletal tissues, which has not been observed in either man or animals (Wrenn et al. 1985).

Uranium is a nephrotoxin, exerting its toxic effect by chemical action mostly in the proximal tubule in humans and animals.

Numerous intermediate-duration uranium exposure studies in animals show that the most sensitive effect is renal toxicity (Dygert 1949a, 1949b, 1949c; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein 1949a, 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953). Dogs and rabbits appear to be the most sensitive species while rats are less sensitive. Susceptibility also depends on the chemical form of the uranium, the more water-soluble compounds being more toxic than the insoluble compounds. Nephrotoxic effects found in these animals range from minimal tubular lesions without functional effects to proteinuria, acute tubular necrosis, and renal failure.

Calculations

Since inhalation MRL's are derived for continuous exposure, the animal NOAEL derived from an intermittent exposure must be adjusted to continuous exposure:

For an exposure of 6 hours a day, 6 days a week,

$(1.1\ mg/m^3) * (6/24) * (6/7) = 0.2357\ mg/m^3$ adjusted to continuous exposure.

The adjusted animal $NOAEL_{(ADJ)}$ must be converted to Human Equivalent Concentration ($LOAEL_{HEC}$) before applying uncertainty factors (UFs) adjustments (EPA 1994) for the derivation of the inhalation MRL:

$$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times RDDR$$

where:

$NOAEL_{[ADJ]}$ = duration adjusted laboratory animal NOAEL (in mg/m^3).
$NOAEL_{[HEC]}$ = human equivalent concentration of adjusted laboratory animal dose (in mg/m^3).
RDDR = Regional Deposited Dose Ratio

Since RDDR values are unavailable for dogs (EPA 1994), ATSDR used a default uncertainty factor of 3 for extrapolating from animals to humans as it incorporates the differences in physiology between dogs and humans. A default factor of 3 was used rather than the standard factor of 10 because of similarities in renal physiology between the two species, i.e., both acidify the urine by active transport of bicarbonate. An additional uncertainty factor of 10 for human intraspecies variability is used to calculate the intermediate-duration inhalation MRL:

$$Intermediate\ Inhalation\ MRL = \frac{NOAEL_{(HEC)}}{\prod UF\ Adjustments}$$

Therefore,

$$Intermediate\ Inhalation\ MRL = \frac{0.2357\ mg/m^3}{30} = 8 \times 10^{-3}\ mg/m^3.$$

Agency Contact (Chemical Manager): Sam Keith.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Uranium (Soluble forms)
CAS number: Multiple
Date: July 2001
Profile status: Final
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [ ]Intermediate [x] Chronic
Key to figure: 112
Species: Dog

MRL: $3x10^{-4}$ [ ] mg/kg/day [ ] ppm [x] mg/m^3

Reference: Stokinger 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: (human study details or strain, number of animals per exposure/control group, sex, dose administration details):

Dogs of both sexes (11-12 M, 9-10 F) were exposed to uranium tetrachloride in inhalation chambers for 6 hours a day, M-F and 3 hours on Saturday (5.5 days a week) for 1 year at concentrations of 0, 0.05, and 0.20 mg U/m^3. (Doses were analytically determined, not estimated.) The activity median aerodynamic diameter (AMAD) of the aerosols was 1–2 µm. 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.

Effects noted in study and corresponding doses: All dogs survived the 1-year exposure period. No significant changes were observed in blood non-protein nitrogen, hematology, histopathology of liver, body weight, or urinary proteins. "Very slight" renal damage as reported in animals exposed to 0.20 mg U/m^3. Histological and biochemical examinations revealed a NOAEL level of 0.05 mg U/m^3 and minimal microscopic lesions in the renal tubules in the 0.20 mg U/m^3 dose level dogs. No significant weight loss was observed in the dogs.

Dose endpoint used for MRL derivation:

[x] NOAEL [] LOAEL

0.05 mg/m^3; (minimal microscopic lesions in the renal tubules in dogs of both sexes at a LOAEL of 0.20 mg U/m^3).

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [x] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

Modification factors used in MRL derivation:

[ ] 1 [ ] 3 [ ]10

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

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
See calculations.

Was a conversion used from intermittent to continuous exposure?
Yes. See calculations.

Other additional studies or pertinent information that lend support to this MRL:
The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) stated that limits for natural (and depleted) uranium in drinking water (the most important source of human exposure) should be based on the chemical toxicity rather than on a hypothetical radiological toxicity in skeletal tissues, which has not been observed in either man or animals (Wrenn et al. 1985).

Uranium has been identified as a weak metal nephrotoxin, exerting its toxic effect by chemical action mostly in the proximal tubule in humans and animals. A study on the kidney functions of uranium mill workers chronically exposed to insoluble uranium (uranium oxide) showed renal tubular dysfunction (as manifested by mild proteinuria, aminoaciduria, and a dose-related clearance of β-2-microglobulin) relative to that of creatinine and the length of time that the uranium workers had spent in the yellowcake (uranium oxides) drying and packaging area. Serum β-2-microglobulin was also elevated in the serum of 22 of the 23 workers tested (Saccomanno et al. 1982; Thun 1985). However, a histopathological autopsy study of individuals, who had been occupationally exposed uranium workers and then spent many years in retirement, found that the damage potentially caused by internalized uranium during their years of occupational exposure had been repaired and was not detectable at death (Russell et al. 1996)

In animal studies, chronic-duration studies with rat and dogs given inhalation uranium (uranium tetrachloride, uranium tetrafluoride, uranyl nitrate hexahydrate, uranium dioxide) doses as low as 0.05 mg U/m^3 and as high as 10 mg U/m^3, administered for 1–5 years suffered nephrotoxicity. Nephrotoxic effects found in these animals ranged from proteinuria and increased bromosulfalein retention (for low doses) (Stokinger et al. 1953) to acute tubular necrosis (for high doses) (Leach et al. 1970). No treatment-related renal effects were seen when Rhesus monkeys and dogs were exposed to uranium dioxide by inhalation at doses as high as 5.1 mg U/m^3 for 1–5 years (Leach et al. 1973). Guinea pigs, mice, rat, cats, rabbits, and dogs (Dygert 1949a, 1949b, 1949c; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein 1949a, 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953), or guinea pigs, rabbits, and rats (Leach et al. 1984; Morrow et al. 1982; Roberts 1949; Stokinger et al. 1953) exposed to these uranium compounds in intermediate- or acute-duration exposure and rats and dogs in chronic-duration studies (Leach et al. 1970; Stokinger et al. 1953) suffered similar kidney damage.

Calculations

Since inhalation MRL's are derived for continuous exposure, the animal NOAEL derived from an intermittent exposure must be adjusted to continuous exposure:

$$NOAEL_{ADJ} = 0.05\ mg\ uranium/m^3\ x\ (\frac{6}{24})\ hours\ x\ (\frac{5.5}{7})\ days = 0.01\ mg\ uranium/m^3.$$

The adjusted animal $NOAEL_{(ADJ)}$ must be converted to Human Equivalent Concentration ($LOAEL_{HEC}$) before applying uncertainty factors (UFs) adjustments (EPA 1994) for the derivation of the inhalation MRL:

$$NOAEL_{[HEC]} = NOAEL_{[ADJ]}\ x\ RDDR$$

where:

$NOAEL_{[ADJ]}$ = duration adjusted laboratory animal NOAEL (in mg/m^3).
$NOAEL_{[HEC]}$ = human equivalent concentration of adjusted laboratory animal dose (in mg/m^3).
RDDR = Regional Deposited Dose Ratio

Since RDDR values are unavailable for dogs (EPA 1994), ATSDR used a default uncertainty factor of 3 for extrapolating from animals to humans as it incorporates the differences in physiology between dogs and humans. A default factor of 3 was used rather than the standard factor of 10 because of similarities in renal physiology between the two species, i.e., both acidify the urine by active transport of bicarbonate. An additional uncertainty factor of 10 for human intraspecies variability is used to calculate the chronic inhalation MRL:

$$Chronic\ Inhalation\ MRL = \frac{NOAEL_{(HEC)}}{\prod UF\ Adjustments}$$

Therefore,

$$Chronic\ Inhalation\ MRL = \frac{0.01\ mg/m^3}{30} = 3\ x\ 10^{-4}\ mg/m^3.$$

Agency Contact (Chemical Manager): Sam Keith.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Uranium
CAS number: Multiple
Date: July 2001
Profile status: Final
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Key to figure: 57
Species: Rabbit

MRL: $2x10^{-3}$ [x] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Gilman AP, Villeneuve DC, Secours VE, et al. 1998b. Uranyl nitrate - 91-day toxicity studies in the New Zealand white rabbit Toxicol Sci. 41(1):129-137, Jan 1998.

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details):

Groups of New Zealand rabbits (10/sex/dose, males 3,200 g, females 3,100 g) were exposed to uranium as uranyl nitrate in drinking water. The males were exposed to 0.96, 4.8, 24, 120, or 600 mg/L for 91 days, while females were exposed only to 4.8, 24 or 600 mg/L. A control group of 10 animals for each sex received tap water without uranyl nitrate (<0.001 mg U/L). All animals were fed chow containing <0.5 µg U/g. Clinical signs were monitored daily, fluid intake and feed consumption were measured 4 times during the experiment and body weights were measured weekly. After 30, 60, and 91 days of exposure, urine was collected from 4 male rabbits in each dosing group and analyzed for uranium, glucose, creatinine, urea nitrogen, total protein, albumin, lactate dehydrogenase (LDH), gamma-glutamyl transpeptidase (gamma-GT), leucine aminopeptidase (LAP), and N-acetyl-β-D-glucosaminidase (NAG). After 30 and 90 days, urine was collected from all 10 female rabbits in the 600 mg/L group and analyzed for glucose, creatinine, urea nitrogen, total protein, albumin, and NAG. Dye clearance tests were performed 1 week prior to termination using standard bromsulfophthalein (BSP) and phenolsulfonphthalein (PSP) test procedures for liver and kidney function, respectively. Four males from each dosing group (3 from group 3) were administered both dyes intravenously and clearance measured; six females from each exposure group were administered the PSP test only. After 91 days, animals were sacrificed and hematological parameters and serum chemistry were analyzed. Organ weights were measured on brain, heart, liver, spleen, and kidney in all groups and the incidence of 12 types of tubular/ interstitial kidney lesions in both females and males were examined. Uranium residues were measured in samples of kidney and femur from 5–6 males in each dosing group and in all female rabbits.

Effects noted in study and corresponding doses: Time-weighted average doses (as mg U/kg/day) calculated by the authors from fluid intake data were: males: 0.05, 0.20, 0.88, 4.82, and 28.70 mg U/kg/day; females: 0.49, 1.32, and 43.02 mg U/kg/day. Four males showed evidence of Pasteurella multocida infection and were excluded from the study. Two other males in the highest dose groups died prematurely, one from apparent mucoid enteritis and one from apparent acute renal failure. Two others were removed after developing hairball obstructions of the GI tract. No evidence of Pasturella infection was observed in the females. No significant differences in weight gain, food consumption or water intake were noted, except that females drank 65% more water than males. These observed hematological and biochemical parameters

did not appear to be dose-dependent. Dose-dependent differences consisted of histopathological changes limited primarily to kidney and were more pronounced in males. In males, a significantly increased incidence of anisokaryosis and nuclear vesiculation was observed in all treated groups, which essentially peaked in the 0.05 and 0.20 mg U/kg/day groups in a threshold-like manner. Nuclear pyknosis, tubular dilation, and atrophy were observed in all treated groups. Hyperchromicity was observed in all treated groups except at 0.05 mg U/kg/day, protein casts in all but the 0.88 mg U/kg/day group, and collagen sclerosis was observed at 0.20, 0.88 and 28.70 mg U/kg/day. Reticulin sclerosis was observed at 0.88, 4.82, and 28.70 mg U/kg/day.

In summary, the following effects were noted in males but not in a dose related manner: (1) renal cytoplasmic vacuolation, anisokaryosis, nuclear vesiculation, nuclear pyknosis, tubular dilatation, tubular atrophy, and reticulin sclerosis were observed at 0.05 mg U/kg/day and above (all dose levels); (2) nuclear hyperchromicity was observed at 0.20 mg U/kg/day and above; and (3) apical displacement of nuclei, protein casts, and collagen sclerosis were observed at low and high doses, but not at some intermediate doses.

The following effects were noted in females but not in a dose related manner: (1) renal cytoplasmic vacuolation, anisokaryosis, nuclear vesiculation, tubular dilation, tubular atrophy, and pigmentation were observed at 0.49 mg U/kg/day and above (all dose levels); (2) nuclear hyperchromicity and collagen sclerosis were observed only at 43.02 mg U/kg/day (highest dose); (3) cytoplasmic inclusions were not observed in any group; and (4) protein casts decreased with dose. The females drank 65% more water than the males, yet appeared to be less affected by the exposure regimen, although they also developed significant tubular nuclear changes in their lowest exposure group. In male rabbits, no urinary parameters were affected after 30 days of treatment. Among males, a significant increase in urinary NAG was observed at 60 days in the 0.88 mg U/kg/day group only, along with a significantly higher total protein in the 28.70 mg U/kg/day group. No parameters were affected at 90 days. No urinary parameters were affected in females. No effect was observed in the BSP dye clearance test (liver function) in male rabbits, however, there was a significant linear relationship between exposure level and the rate of PSP excretion. No effect was observed in females.

Dose endpoint used for MRL derivation: 0.05 mg U/kg/day, renal toxicity. This is considered a minimal LOAEL.

[ ] NOAEL [x] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [x] 3 [ ] 10 (for use of a minimal LOAEL)
[x] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

Modification factors used in MRL derivation:

[ ] 1 [ ] 3 [ ]10

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain:
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:
In other intermediate-duration oral exposures with uranium, dogs exhibited similar to more severe effects at doses of soluble uranium compounds at least one order of magnitude greater and at doses of less soluble compounds several orders of magnitude greater: (1) moderate degeneration of the tubular epithelium of the kidney after a 30-day administration of 15.4 mg U/kg/day as uranyl fluoride or 37.5 mg U/kg/day as sodium diuranate; (2) minimal microscopic lesions in tubular epithelium of the kidney after a 30-day administration of 15.4 mg U/kg/day as uranium tetroxide; (3) minimal microscopic lesions in tubular epithelium of the kidney after a 30-day administration of 15.4 mg U/kg/day as uranium dioxide; (4) severe degeneration changes in tubular epithelium of the kidney after a 30-day administration of 83 mg U/kg/day as uranium trioxide; (5) proteinuria, glucosuria, and minimal microscopic lesions in tubular epithelium of the kidney after a 30-day administration of 5,653 mg U/kg/day as triuranium octaoxide; (6) severe necrotic degeneration in tubular epithelium of the kidney after a 30-day administration of 237 mg U/kg/day as uranyl nitrate hexahydrate; necrosis of the tubular epithelium of the kidney after administration of 313 mg U/kg/day as uranium tetrachloride for 30 days; and (7) increases in blood urea nitrogen, proteinuria, glucosuria, and minimal microscopic lesions in tubular epithelium of the kidney after oral administration with 3,790 mg U/kg/day as uranium tetrafluoride for 30 days (Maynard and Hodge 1949).

In intermediate-duration oral exposures with uranium, rats showed minimal microscopic lesions in tubular epithelium of the kidney after a 30-day administration of 138 mg U/kg/day as uranium tetroxide, 27 mg U/kg/day as uranyl fluoride, 7,859 mg U/kg/day as uranyl acetate dihydrate, 16.6 mg U/kg/day as uranyl nitrate hexahydrate or as uranium tetrachloride; and increases in blood urea nitrogen, proteinuria, glucosuria, and minimal microscopic lesions in tubular epithelium of the kidney after oral administration with 38 mg U/kg/day as ammonium diuranate for 30 days (Maynard and Hodge 1949). Similarly, in a study in which rats were administered 1.5 mg U/kg/day as uranyl nitrate hexahydrate for 15–27 days, desquamation of the tubular epithelium and glomerular degeneration in the kidney of the rats were reported (Goel et al. 1980). Mice also had nodular development on kidney surfaces after administration of single oral doses of 452 U/kg/day as uranyl fluoride for 48 weeks (Tannenbaum and Silverstone 1951). In rabbits, oral administration of uranyl nitrate hexahydrate at a dose of 2.8 mg U/kg/day for 30 days resulted in slight to moderate renal tubular degeneration (Maynard and Hodge 1949).

The MRL level for intermediate-duration oral exposure is also protective for chronic-duration oral exposure. This is because the renal effects of uranium exposure are more dependent on the dose than on the duration of the exposure. Data from a large number of animal studies indicate that renal damage caused by threshold and sublethal doses was overcome and obscured by regeneration of the tubular epithelium, especially in the corticomedullary region, despite continuing exposure (Bentley et al. 1985; Dygert 1949a, 1949b, 1949c; Leach et al. 1984; Maynard and Hodge 1949; Maynard et al. 1953; Pozzani 1949; Roberts 1949; Rothermel 1949; Rothstein 1949c, 1949d; Spiegl 1949; Stokinger et al. 1953). This was also observed among long-term occupational workers whose tissues were histologically evaluated at autopsy (Russell et al. 1996). Such repair, once completed, is histologically indistinguishable from undamaged kidney tissue.

Calculations

The minimal LOAEL of 0.05 mg/kg/day is divided by a total uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability) to calculate the intermediate oral MRL. No adjustment was made for interspecies variation because the rabbit is the most sensitive mammalian species to uranium toxicity and is likely to be more sensitive than humans.

$$\textit{Intermediate Oral MRL} = \frac{\textit{LOAEL}}{\sum \textit{(UF Adjustments)} \; x \sum \textit{(Modification Factor Adjustment}}$$

Therefore,

$$\textit{Intermediate Oral MRL} = \frac{0.05 \;\; mg \,/\, kg \,/\, day}{30} = 2x10^{-3} \;\; mg \,/\, kg \,/\, day$$

Agency Contact (Chemical Manager): Sam Keith.

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

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) 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, minimal risk levels (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 No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(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. When sufficient data exists, 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 Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) 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 2 "18r" data points in Figure 2-1).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "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 regimen 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 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 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, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (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 0.0006 ppm (see footnote "c").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (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 endpoint 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 8 of the profile.

(11) CEL A Cancer Effect Level (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 "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.0006 ppm.

LEGEND

See Figure 2-1

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 intermediate and chronic 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, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. 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 0.0006 ppm (see footnote "c" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level 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

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

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

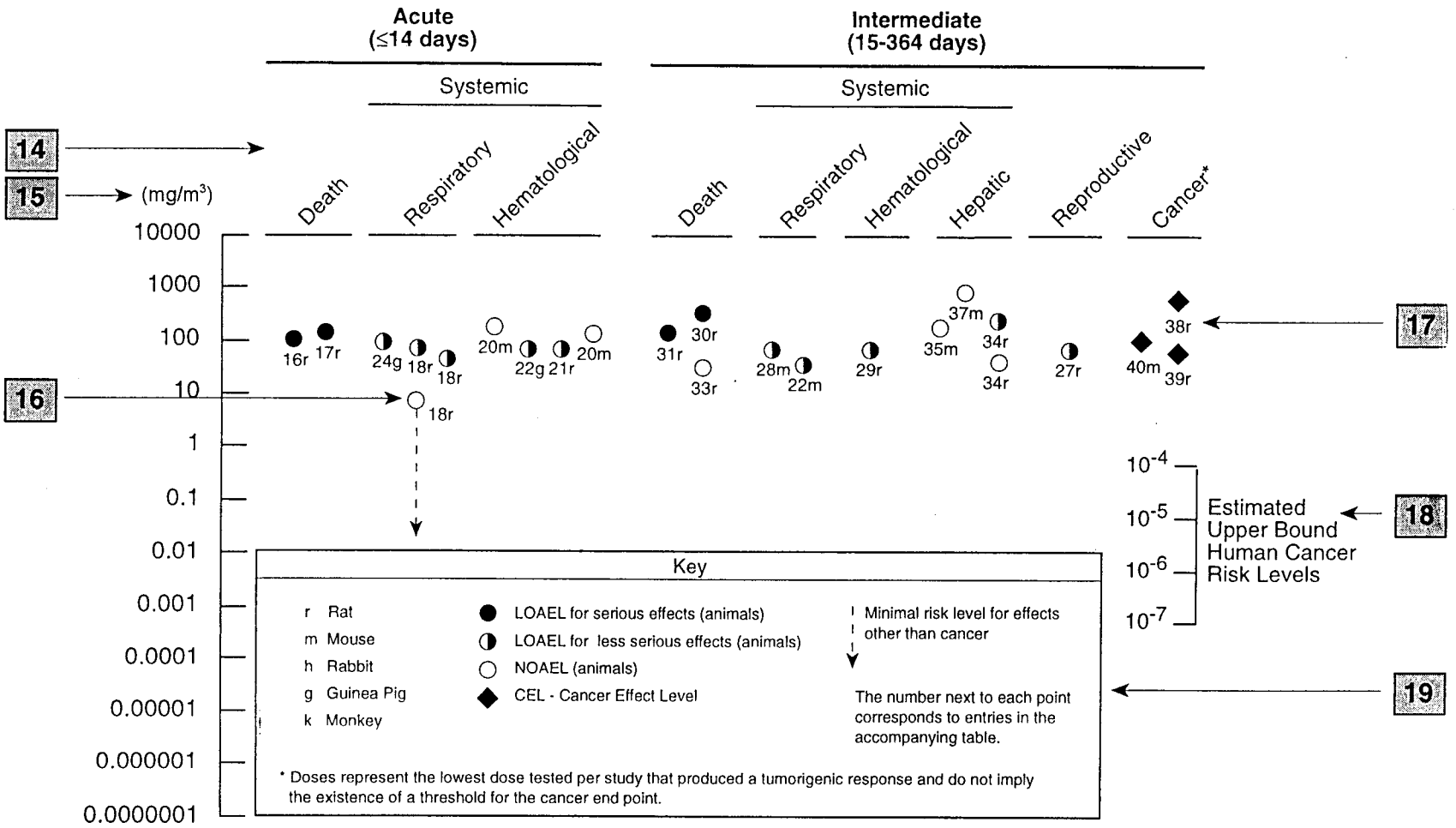
[a] The number corresponds to entries in Figure 2-1.

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-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).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section 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 section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, 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 section. If data are located in the scientific literature, a table of genotoxicity information is included.

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 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (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. They 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 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "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 the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs). To derive an MRL, ATSDR generally selects the most sensitive endpoint 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 endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest 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 LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AMAD	activity median aerodynamic diameter
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
Bq	Becquerel
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Celsius
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
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
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/International 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 or equilibrium factor
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
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
Gy	Gray
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
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_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LET	linear energy transfer
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level

LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
Mg	megagram
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
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
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
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
NR	not reported
NRC	National Research Council; also Nuclear Regulatory Commission
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
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
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
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
QF	Quality Factor
R	Roentgen
RAD	Radiation Absorbed Dose
REL	recommended exposure level/limit
rem	a unit of ionizing radiation, normalized to human tissue response
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short-term exposure limit
STORET	Storage and Retrieval
Sv	Sievert
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act

TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
USNRC	Nuclear Regulatory Commission
UF	uncertainty factor
VOC	Volatile Organic Compound
WHO	World Health Organization
wk	week
WL	Working Level
WLM	Working Level Month
yr	year
>	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

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), 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 stable atoms with particles, such as neutrons or protons, directed at the

stable atoms with high velocity. These artificially produced radioactive elements usually decay by emission of particles, such as 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.

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 (radionuclide) will release energy (decay) in various ways and transform to stable atoms or to other radioactive species called 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 daughter 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 effect 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 that quantity of radioactive material in which there are:

> 1 curie (Ci) = 3.7×10^{10} disintegrations (transformations)/second (dps) or 2.22×10^{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 transformation 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_R, 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 oa a radioisotope, the faster it is decaying.

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

$$A = A_o e^{-0.693t/Trad}$$

where A is the activity in dps or curies or becquerels, A_o is the activity at time zero, t is the time at which measured, and T_{rad} is the radiological half-life of the radionuclide (T_{rad} 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.

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^-)	$5.48x10^{-4}$ amu; 0.51 MeV	–1	0–4 Mev	0–10 m	0–1 cm	Identical to electron
Positron (β^+)	$5.48x10^{-4}$ amu; 0.51 Mev	+1	0-4 Mev	0–10 m	0–1 cm	Identical to electron except for sign of charge
Neutron	1.0086 amu; 939.55 MeV	0	0–15 MeV	b	b	Free half-life: 16 min
X ray (e.m. photon)	–	0	5 keV–100 keV	b	b	Photon from transition of an electron between atomic orbits
Gamma (p) (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 fined as the activity per unit mass or per unit volume. This activity is usually expressed in curies per gram and may be calculated by

$$\text{curies/gram} = 1.3x10^8 / (T_{rad}) \text{ (atomic weight)} \quad \text{or}$$

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

where T_{rad} is 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_{biol}) 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:

$$T_{eff} = (T_{biol} \times T_{rad}) / (T_{biol} + T_{rad}).$$

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 ultraviolet 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) 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 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 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 (&) is a high-velocity electron ejected from a disintegrating nucleus. The particle may be either a negatively charged electron, termed a negatron (&-) or a positively charged electron, termed a positron (&+). Although the precise definition of "beta emission" refers to both &- and &+, common usage of the term generally applies only to the negative particle, as distinguished from the positron emission, which refers to the &+ particle.

D.2.4.2.1 Beta Negative Emission. Beta particle (&-) 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.

[4]Neutrinos also accompany negative beta particles and positron emissions.

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 (&+) is emitted.[4] 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 & 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.

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.

D.3.1 Dose/Exposure Units

D.3.1.1 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 a dose of 1 R is about 0.0096 joules (J) /kg of tissue.

D.3.1.2 Absorbed Dose and Absorbed Dose Rate. The absorbed dose is defined as the energy imparted by the incident radiation to a unit mass of the tissue or organ. The unit of absorbed dose is the rad; 1 rad = 100 erg/gram = 0.01 J/kg in any medium. An exposure of 1 R results in a dose to soft tissue of approximately 0.01 J/kg. The SI unit is the gray which is equivalent to 100 rad or 1 J/kg. Internal and

external exposures from 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 in units of rad/unit time.

D.3.1.3 Working Levels and Working Level Months. 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 daughters (through polonium-214), per liter of air, that will result in the emission of 1.3×10^5 MeV of alpha energy. An activity concentration of 100 pCi radon-222/L of air, in equilibrium with its daughters, corresponds approximately to a potential alpha-energy concentration of 1 WL. The WL unit can also be used for thoron daughters. In this case, 1.3×10^5 MeV of alpha energy (1 WL) is released by the thoron daughters in equilibrium with 7.5 pCi thoron/L. The potential alpha energy exposure of miners is commonly expressed in the unit Working Level Month (WLM). One WLM corresponds to exposure to a 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.3.2 Dosimetry Models

Dosimetry models are used to estimate the dose from internally deposited to 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 and inhalation of low levels of naturally occurring radionuclides as well as radionuclides from nuclear weapons testing.

The models for external dosimetry consider only the photon doses to organs of individuals who are immersed in air or are exposed to a contaminated object.

D.3.2.1 Ingestion. Ingestion of radioactive materials is most likely to occur from contaminated foodstuffs or water or eventual ingestion of inhaled compounds initially deposited in the lung. Ingestion 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.3.2.2 Inhalation. The inhalation route of exposure has 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 of the particles being inhaled. After the particle is deposited, the 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.3.3 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 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.4 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. 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; Hobbs and McClellan 1986; ICRP 1984; Mettler and Moseley 1985; Rubin and Casarett 1968).

D.4.1 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 50–500 rad (0.5–5 Gy), 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 500 rad (5 Gy), 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 or cellular mutations, which may result in abnormal tissue.

D.4.2 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.4.2 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. The development of cancer is not an immediate effect. Radiation-induced leukemia has the shortest latent period at 2 years, while other radiation induced cancers have latent periods >20 years. 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 at any site within the body; 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. However, for effects other than cancer, there is little evidence of human effects at low levels of exposure.

D.5 UNITS IN RADIATION PROTECTION AND REGULATION

D.5.1 Dose Equivalent and Dose Equivalent Rate.

Dose equivalent or rem 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 ICRU has defined the dose equivalent, H, as the product of the absorbed dose, D, and the quality factor, Q, at the point of interest in biological tissue. This relationship is expressed as $H = D \times Q$. The dose equivalent concept is applicable only to doses that are not great enough to produce biomedical effects.

The quality factor 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 Q to define the quantity, rem, which was of use in risk assessment. The generally accepted values for quality factors for various radiation types are provided in Table D-3. The dose equivalent rate is the time rate of change of the dose equivalent to organs and tissues and is expressed as rem/unit time or sievert/unit time.

Table D-3. Quality Factors (Q) and Absorbed Dose Equivalencies

Type of radiation	Quality factor (Q)	Absorbed dose equal to a unit dose equivalent*
X, gamma, or beta radiation	1	1
Alpha particles, multiple-charged particles, fission fragments and heavy particles of unknown charge	20	0.05
Neutrons of unknown energy	10	0.1
High-energy protons	10	0.1

* Absorbed dose in rad equal to 1 rem or the absorbed dose in gray equal to 1 sievert.

Source: USNRC. 1999. Standards for the protection against radiation, table 1004(b).1. 10 CFR 20.1004. U.S. Nuclear Regulatory Commission, Washington, D.C.

D.5.2 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 biologic effect under the same conditions. Gamma rays from cobalt-60 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 quality factor used in calculations of dose equivalents for radiation safety purposes (ICRP 1977; 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.5.3 Effective Dose Equivalent and Effective Dose Equivalent Rate.

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. In an attempt to compare detriment from absorbed dose of a limited portion of the body with the detriment from total body dose, the ICRP (1977) has derived a concept of effective dose equivalent. The effective dose equivalent, H_E, is

$$H_E = (\text{the sum of}) \; W_t \, H_t$$

where H_t is the dose equivalent in the tissue, W_t is the 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). Weighting factors for selected tissues are listed in Table D-4.

The ICRU (1980), ICRP (1984), and NCRP (1985) now recommend that the 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 customary units and the international system of units (SI) for radiological quantities is shown in Table D-5.

Table D-4. Weighting Factors for Calculating Effective Dose Equivalent for Selected Tissues

	Weighting factor		
Tissue	ICRP60	NCRP115/ ICRP60	NRC
Bladder	0.040	0.05	–
Bone marrow	0.143	0.12	0.12
Bone surface	0.009	0.01	0.03
Breast	0.050	0.05	0.15
Colon	0.141	0.12	–
Liver	0.022	0.05	–
Lung	0.111	0.12	0.12
Esophagus	0.034	0.05	–
Ovary	0.020	0.05	–
Skin	0.006	0.01	–
Stomach	0.139	0.12	–
Thyroid	0.021	0.05	0.03
Gonads	0.183	0.20	0.25
subtotal	0.969	1	0.70
Remainder	0.031	0.05	0.30

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.
NRC = Nuclear Regulatory Commission, Title 10, Code of Federal Regulations, Part 20

Table D-5. Comparison of Common and SI Units for Radiation Quantities

Quantity	Customary units	Definition	SI units	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 (Š)	rad per second (rad s^{-1})	10^{-2} $Jkg^{-1}s^{-1}$	gray per second (Gy s^{-1})	Jkg^{-1} s^{-1}
Dose equivalent (H)	rem (rem)	10^{-2} Jkg^{-1}	sievert (Sv)	Jkg^{-1}
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}
Linear energy transfer (LET)	kiloelectron volts per micrometer (keV μm^{-1})	1.602×10^{-10} Jm^{-1}	kiloelectron volts per micrometer (keV μm^{-1})	1.602×10^{-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

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