TUNGSTEN A-1

# 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 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 a hundredfold 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, 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, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

TUNGSTEN B-1

### 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) <u>Health Effect</u>. 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) <u>Key to Figure</u>. 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) <u>System.</u> 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) <u>NOAEL</u>. 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) <u>LOAEL</u>. 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) <u>Reference</u>. The complete reference citation is given in Chapter 9 of the profile.
- (11) <u>CEL</u>. 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) <u>Footnotes</u>. 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) <u>Exposure Period</u>. 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) <u>Health Effect</u>. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) <u>Levels of Exposure</u>. 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<sup>3</sup> or ppm and oral exposure is reported in mg/kg/day.
- (16) <u>NOAEL</u>. 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) <u>CEL</u>. 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) <u>Estimated Upper-Bound Human Cancer Risk Levels</u>. 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<sub>1</sub>\*).
- (19) <u>Key to LSE Figure</u>. The Key explains the abbreviations and symbols used in the figure.

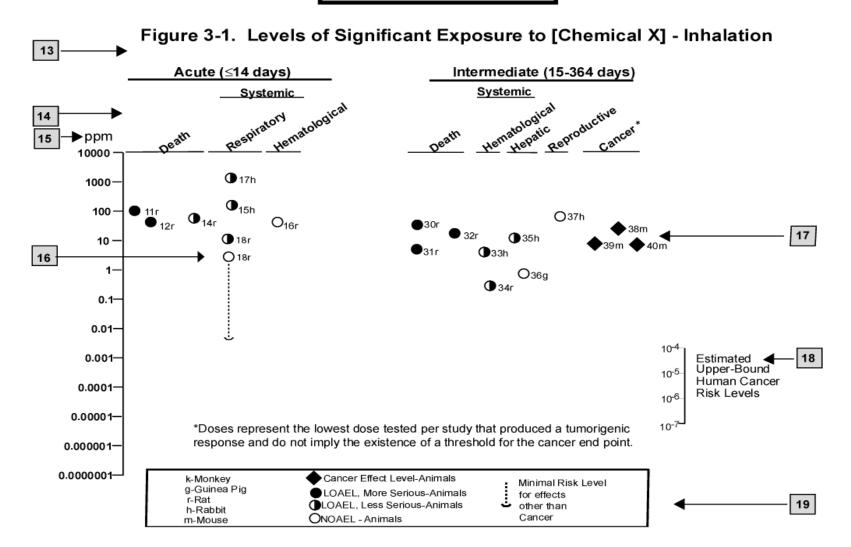


Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

			Exposure			LOAEL (effect)		_	
	Key to figure <sup>a</sup>	Species	frequency/ duration	System	NOAEL (ppm)	Less serio (ppm)	us	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							_	
	0	5	6	7	8	9			10
3 →	Systemic	$\downarrow$	$\downarrow$	<b>\</b>	$\downarrow$	<b>\</b>			<b>\</b>
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	<b>3</b> <sup>b</sup>	10 (hyperpl	lasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE								
	Cancer						11		
							$\downarrow$		
	38	Rat	18 mo 5 d/wk 7 hr/d				20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 <sub>wk</sub> 5 d/wk 6 hr/d				10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 <sub>wk</sub> 5 d/wk 6 hr/d				10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

<sup>&</sup>lt;sup>a</sup> The number corresponds to entries in Figure 3-1.
<sup>b</sup> Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5x10<sup>-3</sup> 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



TUNGSTEN C-1

# 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 AML acute mveloid 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

BMD benchmark dose BMR benchmark response

BSC Board of Scientific Counselors

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 ceiling limit value

CLP Contract Laboratory Program

cm centimeter

CML chronic myeloid leukemia

CPSC Consumer Products Safety Commission

CWA Clean Water Act

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

# TUNGSTEN C-2 APPENDIX C

DOT/UN/ Department of Transportation/United Nations/

NA/IMCO 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

F<sub>1</sub> 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

 $\begin{array}{lll} LC & liquid chromatography \\ LC_{50} & lethal concentration, 50\% \ kill \\ LC_{Lo} & lethal concentration, low \\ LD_{50} & lethal dose, 50\% \ kill \\ LD_{Lo} & lethal dose, low \\ LDH & lactic dehydrogenase \\ LH & luteinizing hormone \\ \end{array}$ 

LOAEL lowest-observed-adverse-effect level LSE Levels of Significant Exposure

LT<sub>50</sub> lethal time, 50% kill

m meter

MA trans,trans-muconic acid MAL maximum allowable level

mCi millicurie

MCL maximum contaminant level

# TUNGSTEN C-3 APPENDIX C

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

NOAELno-observed-adverse-effect levelNOESNational Occupational Exposure SurveyNOHSNational Occupational Hazard Survey

NPD nitrogen phosphorus detection

NPDES National Pollutant Discharge Elimination System

NPL National Priorities List

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

# TUNGSTEN C-4 APPENDIX C

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<sub>50</sub> 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

#### **TUNGSTEN** C-5 APPENDIX C

greater than

> <u>></u> = greater than or equal to

equal to < less than

less than or equal to  $\leq$ 

percent % α alpha β beta gamma  $\overset{\gamma}{\delta}$ delta μm micrometer μg microgram

cancer slope factor  $q_1^*$ 

negative positive +

(+)weakly positive result (-)weakly negative result

TUNGSTEN D-1

# APPENDIX D. INDEX

	28, 29, 58
	96, 112, 120
ambient air	
ammonium paratungstate	
anion exchange	96
atomic absorption spectroscopy	115, 119
beneficiation	83
bioaccumulation	94
bioavailability	87, 94, 112
biokinetics	43, 45, 47, 48, 51, 54, 58, 69, 70
biological half-time	41
biomarkers	57, 58, 69, 115, 121
body tissues	57, 108
body weight effects	28, 31
breast milk	57, 108
cancer	5, 12, 16, 22, 30, 56, 64, 65, 68
carcinogen	30, 35
	30
	2, 11, 12, 30, 65, 67, 98, 109, 110, 113, 114
	41, 43, 52, 126
	96
dietary intake	103
	86, 101, 111
DNA	35, 58
drinking water	
	87, 93
fate	3, 111
	57
fractional absorption	45
<del>-</del>	62, 66
	3, 11, 67, 87, 91, 93, 98, 99, 112
<u> </u>	57, 117
	33
•	
<u> </u>	
1	98
<del></del>	23, 24, 33
	30, 109

D-2

# neoplastic 35, 66 odds ratio \_\_\_\_\_\_\_30 particulate-phase 93.94 sorption coefficient 93 tungsten carbide......2, 4, 7, 11, 12, 16, 17, 20, 33, 35, 53, 58, 62, 63, 68, 73, 85, 87, 90, 103, 104, 106, 109, 123, 125 tungsten polyanions .......95