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 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

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

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

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

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

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

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

LEGEND

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

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

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

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

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

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

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

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

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

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

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

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

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

LEGEND

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

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

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

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

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

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

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

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

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

SAMPLE

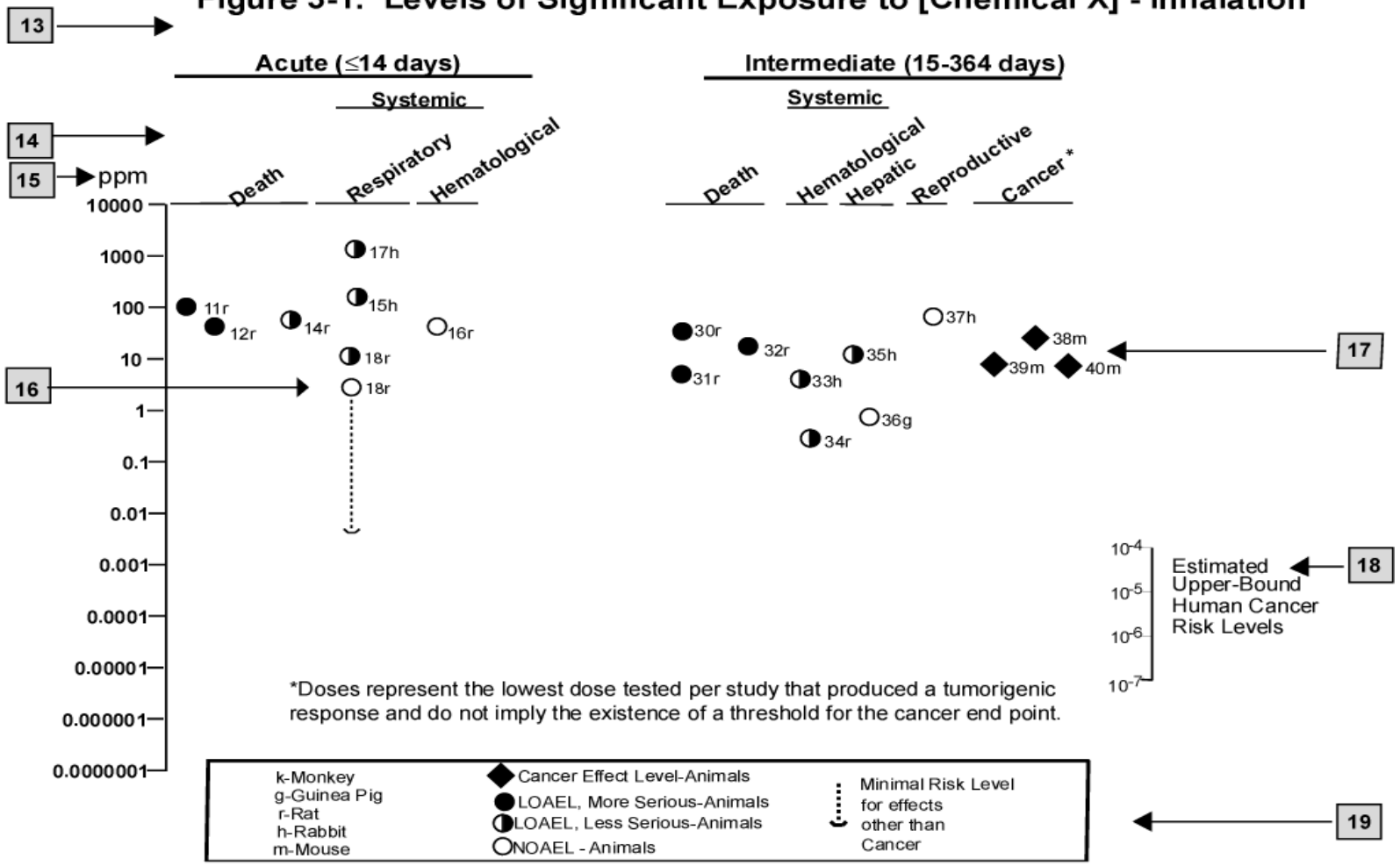
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

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

SAMPLE

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



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
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
CL	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
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code

DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor

MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon

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

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

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APPENDIX D. A FRAMEWORK TO GUIDE PUBLIC HEALTH ASSESSMENT DECISIONS AT LEAD SITES

ABSTRACT

The Agency for Toxic Substances and Disease Registry (ATSDR) provides health consultations and assessments at hazardous waste sites. Many of these sites have potentially significant levels of lead contamination for which the Agency must assess the health implications of exposure. Typically, environmental data are used to predict blood lead (PbB) levels in order to determine at which sites, if any, follow-up action is needed. Estimating blood lead levels from environmental lead concentrations, however, can be problematic. Several approaches have been developed, including classical ingestion rate determinations and comparison to animal studies, prevalence studies extrapolated to comparable sites, regression analysis of known exposure followed by slope factor estimates of similar levels of exposure, and the Environmental Protection Agency's (EPA) Integrated Exposure Uptake Biokinetic Model (IEUBK). Uncertainty is attendant to each of these approaches due, in part, to the limited nature of the environmental sampling data and the various site-specific factors. In this manuscript we describe an approach ATSDR developed to utilize regression analysis with multi-route uptake parameters to estimate blood lead levels.

The profound toxicity of lead has been acknowledged for many years. Developmental effects associated with female lead workers and wives of lead workers were well known during the 18th and 19th centuries, and much of what is taken for granted today regarding lead poisoning in children has been known for more than ninety years. None the less, production of lead compounds, mining and smelting of lead ore and secondary lead sources, and widespread use of lead-containing products continued to increase during the 20th century. These manufacturing, mining, and smelting activities resulted in the contamination of many industrial and residential areas. In addition, leaded gasoline and lead-based paint contributed to the dispersal of lead throughout the environment. During the 1970s and 1980s, federal agencies targeted programs and resources to reduce lead exposure in the United States. These primary prevention activities resulted in regulations governing air emissions, drinking water standards, the phase-out of lead in gasoline, and the banning of lead-based paint and leaded solder. Although these efforts have all contributed to reducing lead exposure to the general population, past uses have resulted in the contamination of many areas, many of which still have the potential for adversely affecting the public health.

Introduction

One of the mandates of the Agency for Toxic Substances and Disease Registry (ATSDR) (under the Comprehensive Environmental Response, Compensation, and Liability Act, Section 104(i)(3), or Superfund) is to address the potential for adverse effects on public health resulting from lead exposure. Lead has been identified as a contaminant in at least 1,026 of the National Priorities List (NPL) sites and is currently ranked first on the Priority List of Hazardous Substances (ATSDR 1996a). Consequently, ATSDR must address public health concerns regarding lead exposure at hazardous waste sites. ATSDR's specific responsibilities related to blood lead screening at lead-contaminated hazardous waste sites include: (1) evaluation of site-specific environmental lead exposure information, (2) identification of populations potentially exposed to lead, (3) decision about whether or not to conduct blood lead screening, (4) evaluation of blood lead screening results, and (5) determination of whether the U.S. Environmental Protection Agency's (EPA) proposed site remediation plans are sufficient to protect public health.

Evaluation of these environmental data is associated with a high level of biomedical judgment regarding appropriate public health actions. In this manuscript, we describe a framework developed to guide such judgment and one that can be used to evaluate the need for a site-specific public health action, which may include blood lead screening. This approach utilizes regression analysis along with uptake parameters and potential results of exposure in an effort to estimate blood lead levels in at-risk populations.

Superfund specifically directs ATSDR to ascertain significant human exposure levels for hazardous substances. Minimal risk levels (MRLs) were developed as part of the strategy to address this mandate. An MRL is "an estimate of the daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse, noncancerous effects over a specified duration of exposure" (ATSDR 1996b) and is analogous to the reference doses and the reference concentrations developed by EPA. MRLs are derived from no-observed-adverse-effect levels or lowest-observed-adverse-effect levels and are intended to assist in determining the safety of communities near hazardous waste sites. For example, an exposure level below the MRL suggests that there is little likelihood of adverse, noncancer human health effects occurring, whereas an exposure level exceeding the MRL alerts the health assessor that a more detailed evaluation using site-specific and chemical-specific information is required. Although the database for lead is large, empirical data from which to obtain a threshold for the effects of lead are lacking. With no observable threshold yet identified, the derivation of conventional health assessment tools such as MRLs is not feasible (De Rosa et al. 1991). In addition, a great deal of the human health effects data are expressed in terms of blood lead (PbB) levels rather than exposure dose, the usual comparison value. Using more traditional methodologies would overlook this significant body of literature, as well as the Centers for Disease Control (CDC, now the Centers for Disease Control and Prevention) guidelines[1]. A predictive tool relating environmental levels to PbBs is needed.

In response to this mandate, the Agency has been seeking ways to further refine the tools necessary for assessing the public health implications from exposure to hazardous substances. MRLs provide a guidance for single routes of exposure to a single substance. But, clearly, multi-route, multi-substance exposure considerations are needed not only for lead but for other substances. To this end, a framework for determining significant human exposure levels was developed (Mumtaz et al. 1995). The development of health-based guidance for lead is consistent with this concept. It should be noted that this effort and others to associate environmental levels with PbBs and consequently make health decisions are simply screening tools. Many issues must be considered on a site-by-site basis and used in conjunction with this guidance. Some of these issues are outlined below.

Exposure and Bioavailability Issues. Primary routes of exposure to lead are via inhalation and ingestion. Lead exposure occurs through inhalation of airborne lead particles with deposition rates in adults of 30%–50% depending on factors such as particle size and ventilation rate (EPA 1986). Once deposited in the lower respiratory tract, lead appears to be almost completely absorbed (Morrow et al. 1980).

Oral intake of lead is a more important route of exposure for children and can occur from ingestion of contaminated food, soil, dust, water, or lead-based paint chips. For young children (1–6 years of age), soil and dust are important pathways for exposure. Ingestion of soil and dust can occur through normal hand-to-mouth activity. Lead-based paint, often found in older homes, and flaking or peeling off walls, can also contribute significantly to exposure in young children. Through normal aging and weathering, intact lead-based paint can contribute to the contamination of dust or soil

The extent and rate of gastrointestinal absorption of lead is mediated by several factors including fasting, physical and chemical form of lead, and dietary status of the individual (Aungst et al. 1981; Grobler et al. 1988; Baltrop and Meek 1979; Chamberlain et al. 1978; Mahaffey et al. 1982; Rabinowitz et al. 1976).

Animal studies indicate that nutritional deficiencies in a number of essential elements (e.g., calcium, iron, zinc, copper, phosphorus) may impact the toxicokinetic and toxicological behavior of lead (ATSDR 1993; Chaney et al. 1989). In infants and children, lead retention has been shown to be inversely correlated with calcium intake (Johnson and Tenuta 1979; Sorrell et al. 1977; Ziegler et al. 1978). Zinc has been

[1]The weight of evidence suggests that PbBs of "10–15 µg/dL and possibly lower" are the levels of concern (ATSDR 1993; Davis 1990; EPA 1986). The Department of Health and Human Services (DHHS) has determined that primary prevention activities should begin at blood lead levels of 10 µg/dL in children (CDC 1991).

shown to have a protective effect against lead toxicity in a number of animal species (Goyer 1986; Haeger-Aronsen et al. 1976; Brewer et al. 1985; Cerklewski and Forbes 1976).

The physical and chemical characteristics of the lead/soil matrix and the particular lead species have also been shown to affect the bioavailability of lead. Studies measuring lead concentration at various soil and dust particle sizes have shown that higher lead concentrations are often found in the smaller-sized fractions. The results of these studies have been summarized by Duggan and Inskip (1985). This is particularly important for young children because smaller particles (<100 μm in diameter) also tend to adhere more readily to hands. Additionally, lead from smaller particles is more readily absorbed from the gastrointestinal tract (Baltrop and Meek 1979). It has been suggested that lead at mining waste sites is less bioavailable and therefore poses less of a human health hazard than lead found at smelter sites or in urban areas (Hemphill et al. 1991; Steele et al. 1990). These differences in bioavailability have been attributed to these biochemical/ biophysical differences of the lead source. Lead particles at mining sites are typically of larger size and consist of the less soluble lead sulfides. However, recent data suggest that this may not always be the case and that a site-by-site evaluation is necessary to determine the lead hazards to the surrounding populations (Gulson et al. 1994; Mushak 1991). See Mushak (1991) for a review of physical/chemical issues regarding lead bioavailability.

Age is also an important factor in that young children absorb lead more efficiently than adults (50% versus 15%) (Chamberlain et al. 1978). Fasting has a significant effect on absorption of lead. Retention of ingested lead is about 60% under fasting conditions compared with 4% when lead is ingested with a balanced meal (James et al. 1985).

Behavioral factors must also be considered. The normal hand to mouth activity of young children results in an increase in lead intake from hand soil/dust particles. In addition, children who exhibit pica behavior are at increased risk because they may ingest more lead-contaminated soil/dust. Health assessors should also be aware of distinct sources of lead within a household or community, such as certain hobbies that would expose one to lead (e.g. using molten lead for casting ammunition, leaded solder for making stained glass, leaded glazes for pottery), the use of folk remedies or lead-glazed pottery, or eating imported canned foods that might contain elevated lead from lead solder used in the can seams.

Approach

Numerous longitudinal and cross-sectional studies have attempted to correlate environmental lead levels with blood lead levels (Table 1). These studies have provided a number of regression analyses and corresponding slope factors (δ) for various media including air, soil, dust, water, and food. The specifics of each of these have been extensively discussed and evaluated elsewhere (Brunekreef 1984; Duggan and Inskip 1985; EPA 1986; Reagan and Silbergeld 1990; Xintaras 1992). In an attempt to use this valuable body of data, ATSDR has developed an integrated exposure regression analysis (Abadin and Wheeler, 1993). This approach utilizes slope values from select studies to integrate all exposures from various pathways, thus providing a cumulative exposure estimate expressed as total blood lead.

Table 1. Summary of blood slope factors from various environmental media.

Population	Slope	Comments	Reference
Air Slope Factors	µg/dL per µg Pb/m^3		
Adults; N = 43	1.75 ± 0.35	Experimental study; EPA analysis	Griffin et al. 1975
Adults; N=5	1.59–3.56	Experimental study; EPA analysis	Rabinowitz et al. 1976
Adults; N=10	2.7	Experimental study; EPA analysis	Chamberlain et al. 1978
Children; 1–18 years of age; N=831; 1,074 blood samples	1.92 ± 0.60	Omaha cross-sectional study; smelter	Angle et al. 1984
Children; N=148	2.46 ± 0.58	Belgium cross-sectional study; smelter; EPA analysis	Roels et al. 1980
Children; N=880	1.53 ± 0.064	Kellogg/Silver Valley cross-sectional study; EPA analysis; smelter	Yankel et al. 1977
Adult males; 5 groups, 30/group	2.57 ± 0.04	Cross-sectional study; air concentrations of 1 µg/m^3	Azar et al. 1975
Adult males; 5 groups, 30/group	1.12	Reanalysis of Azar 1975 by Snee 1982; at air concentration of 1 µg/m^3	Azar et al. 1975
Adult males; 5 groups, 30/group	1–2.39	Analysis of Azar 1975 by EPA; at 1 µg/m^3	Azar et al. 1975
Adults; N=44	1.14	Occupational longitudinal study over 30 months; air concentration <30 µg/m^3	Hodgkins et al. 1992

Table 1. Summary of blood slope factors from various environmental media (continued).

Population	Slope	Comments	Reference
Water Slope Factors	µg/dL per µg Pb/L		
Infants, N=131	0.26 at <15 µg/L 0.04 at >15 µg/L	Scottish study of infants; EPA analysis	Lacey et al. 1985
Children, N=495	0.16 at <15 µg/L 0.03 at >15 µg/L	Scottish study; EPA analysis	Laxen et al. 1987
Adult males, N=7,735	0.06	24 British towns sampled; water lead levels <100 µg/L	Pocock et al. 1983
Adult Females, N=114	0.03	Duplicate diet study; Ayr, Scotland; EPA analysis	Sherlock et al. 1982
Diet Slope Factors:	µg/dL per µg Pb/day		
Infants and toddlers; N=29	0.24	Breast-fed and formula-fed; EPA analysis	Ryu et al. 1983; EPA 1990
Adults; N=31	0.034--females	Duplicate diet study; Ayr, Scotland	Sherlock et al. 1982
Adults; N=15	0.014–0.017--males 0.018–0.022--females	Experimental study; blood leads were not allowed to equilibrate	Stuik et al. 1974
Adult males; N=15	0.027	Experimental study	Cools et al. 1976

Table 1. Summary of blood slope factors from various environmental media (continued).

Population	Slope	Comments	Reference
Soil Slope Factors	µg/dL per µg Pb/kg		
Mixed	0.002–0.016	Review of the literature	Reagan and Silbergeld 1990
Children; 1–18 years of age; N=831; 1,074 blood samples	0.0068 ± 0.00097	Omaha study; urban/suburban	Angle et al. 1984
Children; 1–72 months of age; N=377; 926 blood leads	-0.00016–0.00223 (near house) 0.00073–0.0023 at curb)	New Haven, CT; EPA analysis. The largest slopes were from the children under 1 year	Stark et al. 1982
Children; N=880	0.0011 (avg. for all ages) 0.0025 (for 2–3 year olds)	Kellogg/Silver Valley cross-sectional study; smelter; EPA analysis	Yankel et al. 1977
U.S. males age 18–65 years old (NHANES III)	0.001–0.003	Slope derived from Monte Carlo analysis	Stern 1996
Dust Slope Factors:	µg/dL per mg Pb/kg		
Children; 1–18 years of age; N=831; 1074 blood samples	0.00718 ± 0.00090	Omaha study; urban/suburban; housedust	Angle et al. 1984
Children; 1–6 years of age; N=32	0.008	Homes of lead workers; housedust	Baker 1977
Children; 2 years of age; N=82	0.004	Area of high lead soil; housedust	Baltrop et al. 1974
Adults and children; N=80	0.0086–0.0096 (housedust); 0.0021–0.0067 (outside dust)	Smelter	Roberts et al. 1974
Children; N=377; 1–72 months of age; 926 blood lead levels	0.00402 ± 0.0017 (0–1 year old); 0.00182 ± 0.00066 (2–3 years old) 0.00022±0.00077 (4–7 years old)	New Haven, CT; EPA analysis	Stark et al. 1982

Source: adapted from Duggan and Inskip 1985; EPA 1986, 1989

The general form of the model is:

$PbB=\delta_S TPb_S + \delta_D TPb_D + \delta_W TPb_W + \delta_{AO} TPb_{AO} + \delta_{AI} TPb_{AI} + \delta_F TPb_F$

where,

Pb_S=soil lead concentration
Pb_D=dust lead concentration
Pb_W=water lead concentration
Pb_{AO}=outside air lead concentration
Pb_{AI} = inside air concentration
Pb_F=food lead concentration
T=relative time spent
δ=the respective slope factor for specific media

A worktable that can be used to calculate a cumulative exposure estimate on a site-specific basis is provided in Table 2. To use the table, environmental levels for outdoor air, indoor air, food, water, soil, and dust are needed. In the absence of such data (as may be encountered during health assessment activities), default values can be used. In most situations, default values will be background levels unless data are available to indicate otherwise. Based on the U.S. Food and Drug Administration's (FDA's) Total Diet Study data, lead intake from food for infants and toddlers is about 5 µg/day (Bolger et al. 1991). In some cases, a missing value can be estimated from a known value. For example, EPA (1986) has suggested that indoor air can be considered 0.03 x the level of outdoor air. Suggested default values are listed in Table 3.

Empirically determined and/or default environmental levels are multiplied by the percentage of time one is exposed to a particular source and then multiplied by an appropriate regression slope factor. This assumes slope factor studies were based upon continuous exposure. The slope factors can be derived from regression analysis studies that determine PbBs for a similar route of exposure. Typically, these studies identify standard errors describing the regression line of a particular source of lead exposure. These standard errors can be used to provide an upper and lower confidence limit contribution of each source of lead to PbB. The individual source contributions can then be summed to provide an overall range estimate of PbB. While it is known that such summing of standard errors can lead to errors of population dynamics, detailed demographic analysis (e.g., Monte Carlo simulations) would likely lead to a model without much utility. As a screening tool, the estimates provided here have much greater utility than single value central tendency estimates, yet still provide a simple-to-use model that allows the health assessor an easy means to estimate source contributions to PbB.

As an example, Table 4 provides environmental monitoring data for a subset of data from the Multisite Lead and Cadmium Exposure Study (ATSDR 1995). Default values are used for air and dietary lead. The data are input as described in equation 1 with suggested slope factors from Table 2. The resulting media-specific contributions to PbB, the range of predicted PbBs, and the actual PbBs are given in Table 5.

The purpose of screening tools, such as MRLs or estimates derived from this approach, is to alert health assessors to substances that may pose risk to the exposed population. In addition, these approaches economize the use of resources by eliminating substances for which there is little likelihood of human

Table 2. Worktable for calculation of PbB from environmental and dietary lead.

Media	Concentration	Relative Time Spent	Slope Factor	Blood Lead	
				Low	High
Outdoor Air					
Indoor Air					
Food					
Water					
Soil					
Dust					
			Total		

Table 3. Suggested default values to be used for missing data.

Media	Default	Reference
Outdoor Air	0.1–0.2 µg/m^3	Eldred and Cahill 1994
Indoor Air	0.03–0.06 µg/m^3 (0.3 x outdoor concentration)	EPA 1986
Food	5 µg/day	Bolger et al. 1991
Water	4 µg/L	EPA 1991
Soil	10–70 mg/kg	Shacklette and Boerngen 1972
Dust	10–70 mg/kg	Shacklette and Boerngen 1972

Table 4. Media concentrations for three sites: A, B, and C.			
	SITE		
Media	A	B	C
Soil (mg/kg)	290	768	580
Dust (mg/kg)	383	580	560
Air (µg/m^3)	0.06-0.2	0.06-0.2	0.06-0.2
Water (µg/L)	1	1	1
Food (µg/day)	5	5	5

Table 5. Contribution of environmental lead to blood lead for three sites: A, B, and C.			
	SITE		
Media	**A** contribution to PbB (µg/dL)	**B** contribution to PbB (µg/dL)	**C** contribution to PbB (µg/dL)
Soil	1.1-2.8	3-7.4	2.3-5.6
Dust	1.7-3.8	2.6-5.7	2.5-5.5
Air	0.1-0.2	0.1-0.2	0.1-0.2
Water	0.26	0.26	0.26
Food	1.2	1.2	1.2
Predicted range of PbB (µg/dL)	4.4-8.3	7-14.8	6.4-12.8
Actual PbB	4.8	10.6	13.1

Slope values used were based on Angle et al. (1984): soil = 0.0068 ± 3SE; dust = 0.00718 ± 3SE; air = 1.92 ± 3SE.
Slope value for water was 0.26, based on Lacey et al. 1985 (reanalyzed by EPA 1986).
Slope value for food was 0.24, based on Ryu et al. 1983 (reanalyzed by Marcus in EPA 1990).
Default concentrations were used for air and food.

health effects so that efforts can be concentrated on those compounds of importance. Interpretation of the results from Table 5 would indicate that the potential exists that children at sites B and C have elevated PbBs as defined by the CDC guidelines. Further action on these sites would, therefore, be warranted based on the individual site-specific demographic information and the CDC recommended follow-up services. These might include education, follow-up testing, and social services (CDC 1997). Results from site A, however, would indicate to the health assessor that the environmental data would not likely adversely affect PbBs of resident children; resources can then be shifted to the other substances at the site.

Summary and Discussion

A number of methods and models have been used at sites to estimate potential risks from exposure to lead. One method is the use of prevalence data for estimating PbBs. In this case, PbB measurements can be made at a site and extrapolated to other sites with similar environmental and demographic data. Limitations of this method include site-to-site variability with respect to, among other things, children's behavioral patterns, age, and bioavailability issues. Estimation of past exposures can be problematic because of redistribution of Pb out of the blood compartment since PbB is only an indicator of recent exposure (<90 days).

More traditional approaches have calculated exposure doses from a particular medium via a specific route (ATSDR, 1992). Such exposure doses can then be compared with a reference value derived for the same substance via the same route of exposure. Usual assumptions are ingestion rates of 100 mg dust/day and 200 mg soil/day, child body weight of 15 kg, and continuous exposure scenarios. This approach assumes a threshold for the effects of lead and does not reflect the fullest possible use of the wealth of human data on PbBs.

Pharmacokinetic models have been developed that attempt to relate environmental levels to PbBs (Leggett 1993; O'Flaherty 1995). The Integrated Exposure Uptake Biokinetic Model (IEUBK) developed by EPA is one of the most extensive efforts to date to make population-based predictions of PbBs based upon environmental data. The model incorporates both exposure/uptake parameters and a biokinetic component to estimate the PbB distribution in the exposed population (EPA 1994).

The framework described here provides a useful screening tool. Preliminary efforts to test its predictive power have shown promise (unpublished data). The framework's strengths lie in its simplicity and flexibility to take into consideration environmental and biological variability between sites through the selection of slope factors from similar sites. For example, slope factors from a lead mining study can be used to address concerns at a mining community or, as more refined regression coefficients become available, they can be used in a site-specific manner to assist in making appropriate decisions. The framework also offers a simple approach that allows the health assessor to readily identify factors that may be contributing to elevated PbBs. In this manner, it provides for multi-media evaluation of all source contributions and utilizes a basic approach for determining significant human effect levels. This helps the health assessor determine source contributions of most significance and suggests plausible remediation avenues. These insights, coupled with biomedical judgment, can serve as valuable screening tools to identify those sites meriting further evaluation.

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APPENDIX E. INDEX