APPENDIX A

ATSDR MINIMAL RISK LEVEL 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 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.

APPENDIX A

MRL WORKSHEET

Chemical Name: Aldrin
CAS Number: 309-00-2
Date: April, 2002
Profile Status: Third Draft, Post Public
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to Figure: 7m
Species: mouse

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

Reference: Al-Hachim GM. 1971. Effect of aldrin on the condition avoidance response and electroshock seizure threshold of offspring from aldrin-treated mother. Psychopharmacologia 21:370-373.

Experimental design: Pregnant albino mice (7/group) were given aldrin at 0, 2, or 4 mg/kg by gavage during the third trimester of pregnancy for 5–7 days. The 0 mg/kg/day dose group received only corn oil. Litters were weaned at 30 days of age. Three groups of 10 offspring were randomly selected from each group of maternal animals and were subsequently tested for effects of prenatal exposure to aldrin. From the time of weaning until they were 37 days old, the offspring were tested for the acquisition of conditioned avoidance response. On post partum day 38, the offspring were tested for electroshock seizure threshold.

Effects noted in study and corresponding doses: At both 2 and 4 mg/kg/day, offspring showed decreased body weight and increased electroconvulsive shock thresholds. Values at both levels were statistically significant, but the effects seen at 4 mg/kg/day were not of greater magnitude than those seen at 2 mg/kg/day. Conditioned avoidance responding was not affected.

Dose and end point used for MRL derivation: 2 mg/kg/day; decreased body weight and electroconvulsive shock threshold in offspring of treated mice.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
No.

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

Was a conversion used from intermittent to continuous exposure?
No.

Other additional studies or pertinent information that lend support to this MRL: Another study showed developmental toxicity at higher doses of aldrin in mice and hamsters (Ottolenghi 1974). Hamsters showed increased fetal mortality at 50 mg/kg when aldrin was administered on gestation days 7, 8, or 9, and mice showed an increase in the incidence of webbed feet at 25 mg/kg when aldrin was administered on gestation day 9. These results support the developmental toxicity of aldrin. The end points measured in the MRL study may be more sensitive indicators of fetal toxicity than fetal death or malformations.

Agency Contact (Chemical Manager): G. Douglas Hanley

APPENDIX A

MRL WORKSHEET

Chemical Name: Aldrin
CAS Number: 309-00-2
Date: June, 2002
Profile Status: Third Draft, Post Public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to Figure: 21r
Species: rat

Minimal Risk Level: 0.00003 [X] mg/kg/day [ ] ppm

Reference: Fitzhugh OG, Nelson AA, Quaife ML. 1964. Chronic oral toxicity of aldrin and dieldrin in rats and dogs. Food Cosmet Toxicol 2:551-562.

Experimental design: Weanling Osborne-Mendel strain rats (24/dose, evenly divided by sex) were administered aldrin (recrystallized, #99% purity) in the diet at concentrations of 0, 0.5, 2, 10, 50, 100, or 150 ppm for 2 years. Aldrin was dissolved in corn oil prior to mixing in the diet. Feed and water were available *ad libitum*. During the exposure period, the rats were evaluated for body weight (weekly), clinical observations, and mortality; it is unclear how often observations for clinical signs and mortality were made. At the end of the exposure period, surviving rats were sacrificed and autopsied. Animals that died before the end of the first year of exposure were autopsied, but organ weights were not recorded. Only 68% (115/168) of the rats in the study were examined microscopically; most of these only had the liver, kidneys, testes, and gross lesions or tumors examined. The other animals had a more extensive histopathological examination that included lung, heart, liver, spleen, pancreas, stomach, small intestine, colon, kidney, adrenal gland, thyroid, tumors, and gross lesions; additionally, the urinary bladder and prostate were frequently examined.

Effects noted in study and corresponding doses: Significant increases in liver to body-weight ratio and hepatic histopathological changes consistent with exposure to chlorinated hydrocarbons were observed at doses as low as 0.5 ppm. The hepatic lesions at 0.5 and 2 ppm were slight (e.g., enlarged centrilobular hepatocytes with cytoplasmic eosinophilia somewhat increased, and peripheral migration of the basophilic granules along with less prominent alterations of cytoplasmic vacuolation and bile duct proliferation), but progressed in severity with increasing dose. At 10 ppm, an increase in vacuolation of hepatic cells was observed. Survival was reduced at 50 ppm and above, and distended and hemorrhagic bladders were seen in males dying before termination of the study. In animals exposed to 100 and 150 ppm, an increase in the severity of nephritis was observed. This occurred predominantly in males. Reassessment of the renal histopathology data by Reuber (1980) found that male rats ingesting 10 ppm and above had an increased incidence and greater severity of nephritis than did control animals. Some of the animals that consumed high doses and died early had diffuse necrosis of the renal tubules.

A number of the changes at 0.5 ppm are consistent with a marked hepatic adaptive response associated with induction of the hepatic mixed function oxidase system and proliferation of smooth endoplasmic reticulum. The observation of hepatocellular hypertrophy is consistent with adaption. Increased cytoplasmic eosinophilia in this case is likely associated with the adaptive response of marked proliferation of the smooth endoplasmic reticulum (SER). The peripheralization of cytoplasmic basophilic granules is most likely the result of outward compression of detached ribosomes by massively expanding SER. Ribosomal detachment has been observed in chlorinated hydrocarbon toxicity. Cytoplasmic vacuolation is a common manifestation of cellular degeneration. Bile duct proliferation is

known to occur in response to chronic toxic injury. Modifications occurring in the mixed function oxidase system consequent to the adaptive response may result in its functional enhancement or neutralization. This in turn has the consequence of potentiating or inhibiting toxic responses to other exogenous substances. While the mechanism of aldrin-mediated hepatotoxicity has not been elucidated, the adaptive response is considered to be an adverse effect of aldrin. The cellular adaption that results from aldrin toxicity creates a liver that potentially has a tremendously heightened state of metabolic activity, which correspondingly may have a similarly heightened capacity to toxify or detoxify upon continued exposure to aldrin.

Dose and end point used for MRL derivation: 0.5 ppm (0.025 mg/kg/day); enlarged hepatocyte, increase in cytoplasmic eosinophilia with peripheral migration of basophilic granules, and possible increases in vacuolation and bile duct proliferation.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? ppm doses (mg/kg diet) were multiplied by a food factor of 0.05 kg diet/kg body weight/day (EPA 1986m). The resulting doses were 0, 0.025, 0.1, 0.5, 2.5, 5, and 7.5 mg/kg/day.

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?
No.

Other additional studies or pertinent information that lend support to this MRL: Other adverse hepatic effects observed in chronic-duration studies with aldrin include hyaline droplet degeneration in dogs that ingested 0.12–0.25 mg/kg/day of aldrin for 15.7 months (Treon et al. 1955b) and slight-to-moderate fatty degeneration in dogs exposed to 1 mg/kg/day of aldrin for 25 months (Fitzhugh et al. 1964). These studies are, however, limited in that the number of dogs tested was quite small. Several chronic duration studies with dieldrin also showed adverse hepatic effects. Rats exposed to 0.16–0.063 mg/kg/day dieldrin throughout their lifetime were reported to have hepatic lesions consisting of centrilobular degeneration and peripheral hyperplasia (Harr et al. 1970), but incidence data and statistical analyses were not provided to support this conclusion and the use of a semisynthetic diet may have compromised the rats. Also mice exposed to 1.3 mg/kg/day dieldrin for 2 years had livers with occasional necrotic areas (Thorpe and Walker 1973), but incidence was not reported and it is unclear whether the necrotic areas were secondary to tumor development. In the 2-year study used to derive the MRL for dieldrin, absolute and relative liver weights were increased in female rats at $0.05 mg/kg/day, and liver parenchymal cell changes, "considered to be characteristic of exposure to organochlorine insecticide" but not otherwise specified, were increased at 0.5 at mg/kg/day.

The chronic oral MRL is the same as the EPA RfD for aldrin (IRIS 2002a), as the value ($3x10^{-5}$ mg/kg/day) is based on the same study (Fitzhugh et al. 1964), species (rat), end point (liver

effects), and effect level (0.025 mg/kg/day LOAEL). The chronic oral MRL remains the same as that reported previously by ATSDR (1993).

Agency Contact (Chemical Manager): G. Douglas Hanley

APPENDIX A

MRL WORKSHEET

Chemical Name: Dieldrin
CAS Number: 60-57-1
Date: June, 2002
Profile Status: Third Draft, Post Public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to Figure: 44K
Species: monkey

Minimal Risk Level: 0.0001 [X] mg/kg/day [ ] ppm

Reference: Smith RM, Cunningham WL, Van Gelder GA. 1976. Dieldrin toxicity and successive discrimination reversal in squirrel monkeys (*Saimiri sciureus*). J Toxicol Environ Health 1:737-747.

Experimental design: Technical dieldrin was dissolved in absolute ethanol and injected into marshmallows in 10 µL amounts, which resulted in doses of 0.01 or 0.1 mg dieldrin/kg/day when fed to squirrel monkeys. The low- and high-dose groups consisted of three and four monkeys, respectively; another group of two monkeys served as controls. All monkeys were tested for their ability to learn a visual nonspatial successive discrimination reversal task during a 55-day period of daily dosing with dieldrin.

Effects noted in study and corresponding doses: Signs of impaired learning were apparent within 15 days of treatment initiation in the 0.1 mg/kg/day dose group, and persisted throughout the 55 days of treatment. The monkeys consuming 0.01 mg dieldrin/kg/day did not appear to be adversely affected with respect to learning ability when compared to controls.

Dose and end point used for MRL derivation: 0.01 mg/kg/day; impaired learning of a successive discrimination reversal task.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
No.

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

Was a conversion used from intermittent to continuous exposure?
No.

Other additional studies or pertinent information that lend support to this MRL: The choice of this end point is supported by the study of Burt (1975) in which impaired maze training was noted in rats treated for 60–120 days with a diet containing 5 ppm of dieldrin (converted to a dose of 0.25 mg/kg/day using reference values from EPA 1986m).

Agency Contact (Chemical Manager): G. Douglas Hanley

APPENDIX A

MRL WORKSHEET

Chemical Name: Dieldrin
CAS Number: 60-57-1
Date: June, 2002
Profile Status: Third Draft, Post Public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to Figure: 59r
Species: rat

Minimal Risk Level: 0.00005 [X] mg/kg/day [ ] ppm

Reference: Walker AIT, Stevenson DE, Robinson J, et al. 1969. The toxicology and pharmacodynamics of dieldrin (HEOD): Two-year oral exposures of rats and dogs. Toxicol Appl Pharmacol 15:345-373.

Experimental design: Rats (25/sex/dose; 45/sex/controls) were fed diet containing 0, 0.1, 1.0, or 10.0 ppm dieldrin for 2 years. Based on intake assumptions reported by investigators (1 ppm=0.0475 mg/kg/day in males and 0.0582 mg/kg/day in females), doses were . 0.005, 0.05, and 0.5 mg/kg/day. Study end points included clinical observations, food intake, body weight, clinical chemistry, hematology, urine indices, organ weights, gross pathology, and histology (including liver, heart, lungs, spleen, lymph nodes, stomach, intestines, kidneys, bladder, thyroid, parathyroid, adrenals, pancreas, reproductive tissues, brain, muscle, skin, and eyes). Liver-related clinical chemistry indices included plasma alkaline phosphatase, SGOT, and bile pigments in the urine.

Effects noted in study and corresponding doses: Effects in the rats included increased absolute and relative liver weights in females at $0.05 mg/kg/day. Liver parenchymal cell changes, "considered to be characteristic of exposure to organochlorine insecticide" but not otherwise specified, were increased in high-dose females; total incidences during 2 years of exposure were 0/23, 0/23, 0/23, and 6/23 females at 0, 0.005, 0.05, and 0.5 mg/kg/day, respectively. In males, these liver parenchymal changes were only observed in one high-dose animal (i.e., 1/23 at 0.5 mg/kg/day). Two of the 0.5 mg/kg/day females and one control female also showed focal hyperplasia of the hepatic parenchymal cells, forming microscopic nodules. Other kinds of hepatic lesions (focal parenchymal necrosis, proliferated ductules, focal fibrosis, and/or cystic hyperplasia of intrahepatic bile ducts) were seen in a few rats of both sexes, but were not treatment-related as they were dispersed among the test and control groups (5/23, 0/23, 2/23, and 5/23 in females and 4/43, 0/23, 1/23, and 2/23 in males at 0, 0.005, 0.05, and 0.5 mg/kg/day, respectively). There were no indications of dieldrin-related changes in serum alkaline phosphatase or SGPT, histology of non-liver tissues, or body weight in any of the exposed groups, although irritability, tremors, and occasional convulsions (characteristic signs of dieldrin neurotoxicity) occurred at 0.5 mg/kg/day. These behavioral changes usually occurred during handling, did not progress after 3 months of exposure, and did not affect well-being.

Dose and end point used for MRL derivation: 0.005 mg/kg/day. Liver weight was increased at the LOAEL (0.05 mg/kg/day), with progression to parenchymal cell changes including focal hyperplasia at 0.5 mg/kg/day.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
No. Dietary ppm concentration was converted to mg/kg/day dose using reported intake assumptions as indicated in the experimental design summarized above.

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?
No.

Other additional studies or pertinent information that lend support to this MRL: Other studies in rats and dogs support the choice of liver toxicity as the end point for the chronic oral MRL (Fitzhugh et al. 1964; Harr et al. 1970). Exposure for 2 years caused slight hepatic histopathological changes in rats at 0.025 and 0.1 mg/kg/day that were considered to be adverse effects of dieldrin (Fitzhugh et al. 1964). At 2.5 mg/kg/day and above, the changes were considered to be marked and included an increase in the severity of hepatic cell vacuolation. In the Harr et al. (1970) study, centrilobular degeneration and pyknosis of hepatic cell nuclei were reported in rats fed "critical levels of dieldrin" (0.016–0.063 mg/kg/day) throughout their lifetimes. However, the specific doses at which these effects were observed were not noted. Chronic studies in dogs also indicated that dieldrin produced degenerative effects in the liver (Fitzhugh et al. 1964; Kitselman 1953). In the Fitzhugh et al. (1964) study, a slight fatty change in the liver and a slight hepatic cell atrophy was reported at 0.5 mg/kg/day. This study was limited, however, in that no controls were used and only 1–2 males and females per dose were tested. In Kitselman (1953), slight degeneration of the liver was reported in one of three dogs fed 0.2 mg/kg/day and in all three dogs fed 0.6 mg/kg/day for a year. This study is also limited in that too few animals were tested (a total of three dogs per dose), replacement dogs were used, and details of the study protocol were incomplete.

The chronic oral MRL is the same as the EPA RfD for dieldrin (IRIS 2002b), as the value ($5x10^{-5}$ mg/kg/day) is based on the same study (Walker et al. 1969), species (rat), end point (liver effects), and effect level (0.005 mg/kg/day NOAEL). The basis of the MRL (species and end point) differs from that used in the previous version of the ATSDR profile (ATSDR 1993), although the actual value (5×10^{5} mg/kg/day) is unchanged. The basis of the MRL has been changed to address misinterpretations of the critical study in the previous ATSDR profile (ATSDR 1993).

The MRL was previously based on a NOAEL of 0.005 mg/kg/day for liver effects in dogs from the Walker et al. (1969) study. In the dog study, groups of five males and five females were given capsules containing 0, 0.005, or 0.05 mg/kg/day dieldrin for 2 years. The study end points were essentially the same as in the Walker et al. (1969) rat study, but additionally included assessments of SGPT, BSP clearance (control and high-dose groups), and neurology (EEG recordings in control and high-dose groups). Effects in the dogs occurred at 0.05 mg/kg/day and included increased absolute and relative liver weights in females, increased serum alkaline phosphatase in males and females beginning after 30 weeks of exposure, and decreased total serum proteins in males. There were no changes in histology of the liver or other tissues, histochemical distribution of fat or alkaline phosphatase activity in the liver, or liver function as assessed by BSP clearance. The origin of the increased serum alkaline phosphatase

activity was unknown, but was not believed to be due to bone disorders or biliary obstruction (i.e., the usual clinical interpretation of elevated serum alkaline phosphatase in dogs [Cornelius 1970; Walker et al. 1969]). The decrease in total serum proteins was slight and considered to have no clinical or toxicological significance since the electrophoretic pattern of the proteins was unchanged. There were no exposure-related behavioral changes as found in the rats. ATSDR (1993) previously interpreted the high dose in dogs (0.05 mg/kg/day) as a LOAEL for liver effects based on the increases in liver weight and serum alkaline phosphatase, and used the NOAEL (0.005 mg/kg/day) to derive the MRL. Considering the lack of histological changes in the liver, evidence that the increased serum alkaline phosphatase is not liver-related, and lack of effect on liver function as assessed by BSP clearance, as well as the investigators' conclusions that there were no histopathologic liver lesions attributable to dieldrin in the dogs, the evidence indicates that 0.05 mg/kg/day should be classified as a NOAEL rather than a LOAEL. The 0.05 mg/kg/day NOAEL in dogs is not used to derive the MRL, however, because re-evaluation of the rat data shows that this dose is a LOAEL in rats, as discussed below.

ATSDR (1993) previously classified all of the doses in the Walker et al. (1969) rat study as NOAELs. This classification was based on an interpretation that hepatotoxic effects (focal hyperplasia of hepatic parenchymal cells, focal parenchymal necrosis, proliferated ductules, focal fibrosis, and cystic hyperplasia of intrahepatic bile ducts) were observed in both treated and control animals with no indication of an increase in incidence or severity in treated animals. Re-evaluation of the report shows that there are actually two categories of tabulated liver data (i.e., one labeled "Liver[a]" and one labeled "Organochlorine insecticide changes"). The lesions tabulated as "Organochlorine insecticide changes" are in fact liver parenchymal effects that are characteristic of dieldrin and other organochlorine insecticides (and are treatment-related in the dog study), whereas other kinds of liver lesions (i.e., those simply tabulated as "Liver[a]") are the effects that were dispersed throughout the control and treated groups and not attributable to exposure. In other words, ATSDR previously correctly interpreted the "Liver" data as negative, but did not recognize that the other category of liver effects (i.e., the organochlorine insecticide changes) provides positive evidence. This interpretation is supported by the footnote to the "Liver[a]" heading, which states that these liver lesions "...are considered not to be associated with exposure to organochlorine insecticide", the investigators' conclusion that "Histopathologic liver lesions attributable to dieldrin were observed in the rats (10 ppm) but not in dogs", and the fact that the dieldrin-attributable liver effects are discussed in the report text using the incidences from the "Organochlorine insecticide changes" column in the table. Therefore, there is a progression of liver effects as shown by increased liver weight at 0.05 mg/kg/day and histological changes at 0.5 mg/kg/day. Consequently, 0.005 and 0.05 mg/kg/day are reclassified as a NOAEL and LOAEL, respectively, and the NOAEL is used as the basis of the MRL.

Agency Contact (Chemical Manager): G. Douglas Hanley

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 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 chapter. 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 Chapter 3 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, "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 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 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 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.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) 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 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 LSE Table 3-1

(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 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 2 "18r" data points in 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 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 0.005 ppm (see footnote "b").

(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 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 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 "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

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, 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 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

1 6

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

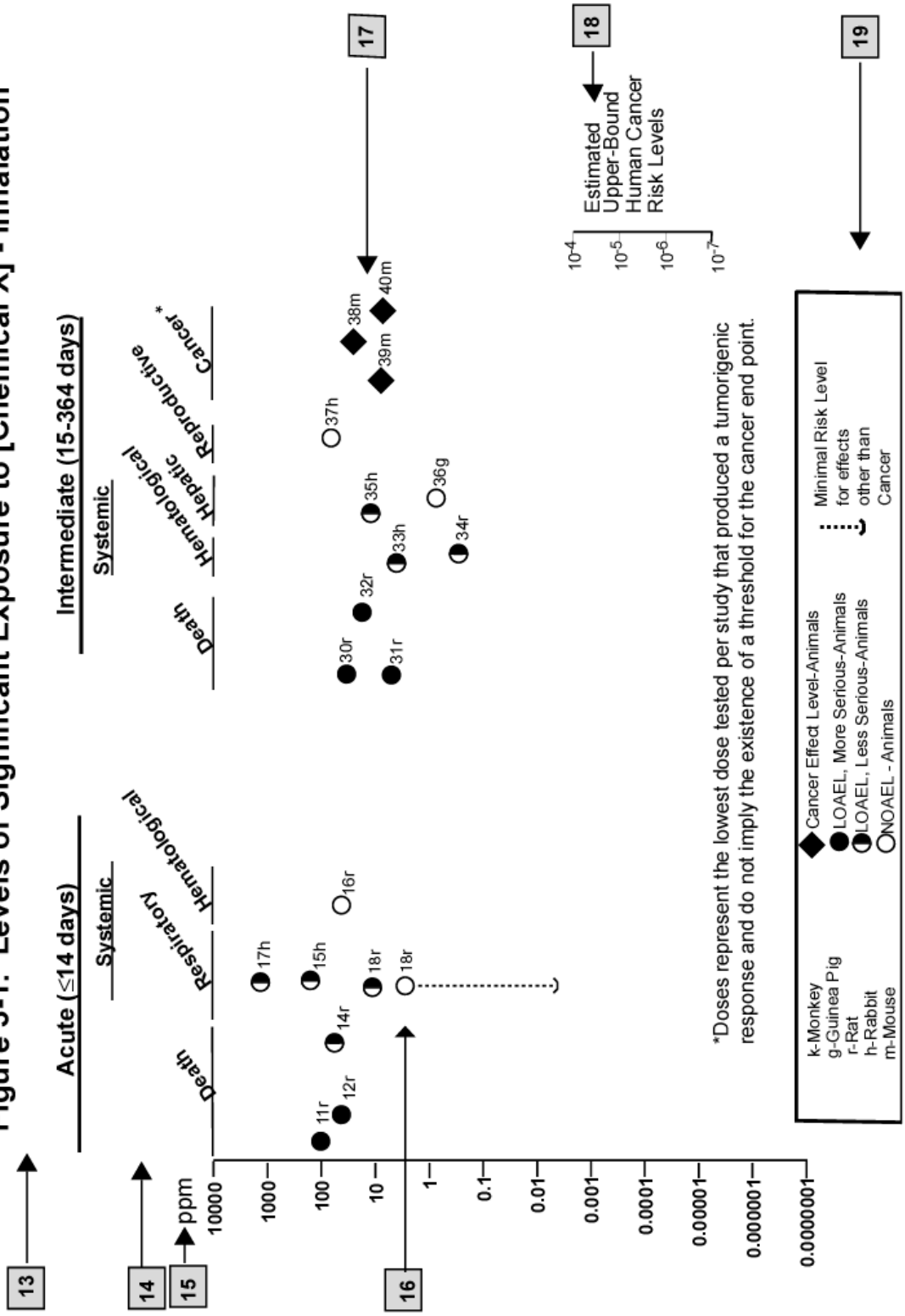
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 6 INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 6 Systemic	9	9	9	9	9		9
4 6 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					9		
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

[a] The number corresponds to entries in Figure 3-1.

12 6 [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).

SAMPLE

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



APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
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
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotranferase
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
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/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_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
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
LDH	lactic dehydrogenase
LH	luteinizing hormone
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
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal

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
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
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
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
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
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
RBC	red blood cell
REL	recommended exposure level/limit
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
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

APPENDIX D

INDEX

APPENDIX D