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.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Fluoride
CAS Number: NA
Date: December 1, 2003
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to Figure: 53
Species: Humans

Minimal Risk Level: 0.05 [X] mg/kg/day [ ] mg/m^3

Reference: Li Y, Liang C, Slemenda CW, et al. 2001. Effect of long-term exposure to fluoride in drinking water on risks of bone fractures. J Bone Miner Res 16:932-939.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Six communities in rural China with different levels of naturally occurring fluoride in the water were examined. The subjects were 50 years and older; the mean ages ranged from 62.6 to 64.0 years. The majority of the subjects had been living in the same community since birth. There was a higher percentage of males in the highest fluoride group (52.4%) than in the other groups (41.8–47.0%). The water fluoride concentrations were 0.25–0.34, 0.58–0.73, 1.00–1.06, 1.45–2.19, 2.62–3.56, and 4.32–7.97 ppm. Three-day dietary surveys were collected for 10% of randomly selected subjects; estimated nutrition levels were adequate for all six populations. None of the subjects used fluoride-containing toothpaste or mouthwashes and there was a minimal use of packaged beverages and canned foods; fluoride levels in brewed tea samples were largely determined by the levels of fluoride in the water. The authors calculated total daily fluoride intakes of 0.7, 2, 3, 7, 8, and 14 mg/day. The subjects self-reported bone fractures. If the fracture received medical attention, then original x-rays were obtained; for other fractures, x-rays were taken to verify self-reported fractures. The reliability of the reported fracture was 99.1%.

Effects noted in study and corresponding concentrations: Age, gender, alcohol consumption, and level of physical activity were significant factors for the risk of overall bone fractures since age 20 years; cigarette smoking and BMI did not significantly alter bone fracture prevalence. The trend for overall bone fracture prevalence (adjusted for age and gender) had a U-shaped pattern. As compared to the 1.00–1.06 ppm group, significantly higher prevalences of bone fracture were found in the lowest (0.25–0.34 ppm fluoride) and highest (4.32–7.97 ppm) groups. The prevalences were 7.41, 6.40, 5.11, 6.04, 6.09, and 7.40%, respectively. When only hip fractures since age 20 were examined, significantly higher prevalences (adjusted for age and BMI) were found in the highest fluoride group, as compared to the 1.00–1.06 ppm group. The prevalences of hip fractures were 0.37, 0.43, 0.37, 0.89, 0.76, and 1.20%, respectively. A similar pattern was observed when overall fractures since age 50 were examined; the prevalences were 4.33, 3.20, 3.28, 3.30, 3.62, and 4.80 ($p=0.02$), respectively. Only a small number of subjects reported spine fractures (49); none of the fluoride groups significantly differed from the 1.00–1.06 ppm group.

Concentration and end point used for MRL derivation:

The MRL is based on a NOAEL of 0.15 mg fluoride/kg/day for increased fracture rate.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL in a sensitive subpopulation
[ ] 10 for extrapolation from animals to humans
[X] 3 for human variability; a value less than 10 was used because the most sensitive population, elderly men and women, were examined.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Yes. Doses were calculated using the reported daily fluoride intakes of 0.7, 2, 3, 7, 8, and 14 mg/day and a reference body weight of 55 kg.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure? NA

Other additional studies or pertinent information that lend support to this MRL: A number of studies have examined the possible association between exposure to fluoridated water and the risk of increased bone fractures, in particular, hip fractures. In general, the studies involved comparing the incidence of hip fractures among residents aged 55 years and older living in a community with fluoridated water (around 1 ppm) with the incidence in a comparable community with low levels of fluoride in the water. Inconsistent results have been found, with studies finding decreases (Lehmann et al. 1998; Phipps et al. 2000; Simonen and Laittinen 1985), increases (Cooper et al. 1990, 1991; Danielson et al. 1992; Jacobsen et al. 1990, 1992; Kurttio et al. 1999), or no effect (Arnala et al. 1986; Cauley et al. 1995; Goggin et al. 1965; Jacobsen et al. 1993; Karagas et al. 1996; Kröger et al 1994; Suarez-Almazor et al. 1993) on hip fracture risk. Studies by Li et al. (2001) and Sowers et al. (1986) have examined communities with higher levels of naturally occurring fluoride in the water. Both studies found increases in the incidence of hip fractures in residents exposed to 4 ppm fluoride and higher (Li et al. 2001; Sowers et al. 1986, 1991); the hip fracture incidence in the highly exposed community was compared to the rates in communities with approximately 1 ppm fluoride in the water. Significant increases in the occurrence of nonvertebral fractures were also observed in postmenopausal women ingesting sodium fluoride (34 mg fluoride/kg/day) for the treatment of osteoporosis (Riggs et al. 1990, 1994). This result was not found in another study of postmenopausal women with spinal osteoporosis treated with 34 mg fluoride/kg/day as sodium fluoride (Kleerekoper et al. 1991). A meta-analysis of these data, as well as other clinical studies, found a significant correlation between exposure to high levels of fluoride and an increased relative risk of nonvertebral fractures (Haguenauer et al. 2000).

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name:	Hydrogen Fluoride
CAS Number:	7664-39-3
Date:	December 1, 2003
Profile Status:	Final
Route:	[X] Inhalation [ ] Oral
Duration:	[X] Acute [ ] Intermediate [ ] Chronic
Key to Figure:	6
Species:	Humans

Minimal Risk Level: 0.02 [ ] mg/kg/day [X] ppm

Reference: Lund K, Ekstrand J, Poe J, et al. 1997. Exposure to hydrogen fluoride: an experimental study in humans of concentrations of fluoride in plasma, symptoms, and lung function. Occup Environ Med 54:32-37.

Lund K, Refsnes M, Sandstrøm T, et al. 1999. Increased CD3 positive cells in bronchoalveolar lavage fluid after hydrogen fluoride inhalation. Scand J Work Environ Health 25:326-334.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Groups of 7-9 healthy, nonsmoking males (21–44 years of age) were exposed to 0.2-0.6, 0.7–2.4, or 2.5–5.2 mg/m^3 hydrogen fluoride for 1 hour. For the last 15 minutes of the exposure, the subjects performed an ergometric test at a fixed work load of 75W. Bronchoalveolar lavage (BAL) was performed 3 weeks prior to exposure and 24 hours after exposure. Lung function tests were performed immediately before exposure, every 15 minutes during exposure, at exposure termination, 30 minutes after exposure, and 1, 2, 3, and 4 hours after exposure. Symptom surveys were completed before exposure initiation, after 30 minutes of exposure, at exposure termination, and 4 and 24 hours after exposure. Eye, upper airway (nose and throat), and lower airway symptoms were scored based on a 5 point scale with 5 being the most severe.

The midpoint of the range of concentrations was used to calculate ppm levels: 0.4 mg hydrogen fluoride/m^3 x 24.45/20 x 19/20 = 0.5 ppm fluoride; 1.7 mg/m^3 = 1.9 ppm, 3.9 mg/m^3 = 4.5 ppm

Effects noted in study and corresponding concentrations: No significant exposure-related alterations in lung function (FEV1 or FVC) were observed and no significant correlations between plasma fluoride concentrations and FVC or FEV1 were found. Increases (as compared to scores prior to exposure) in upper airway symptom scores were observed in the low ($p=0.06$) and high ($p=0.02$) concentration groups and for all concentrations combined ($p<0.001$); similarly, total symptom scores were significantly ($p<0.04$) increased in the low and high concentration groups and all groups combined. The severity of the upper airway score was low (scores of 1–3) in the low exposure group. All subjects reported a change in the upper airway symptom score in the high concentration group; four subjects scored the symptoms as low and three scored them as high. A significant increase in eye symptom score was also observed in all groups combined, but not for individual exposure level groups. The effect of hydrogen fluoride exposure was assessed by comparing the before and after exposure BAL fluid. Significant increases in the percentage of CD3-positive cells were found in the bronchial portion of the mid- and high-dose group and in the bronchoalveolar portion of the high-dose group. A significant increase in the percentage of lymphocytes in the bronchial and bronchoalveolar portions in the mid-concentration group was observed. A significant correlation between the individual changes in the percentage of CD3-positive cells and the changes in the percentage of lymphocytes from the bronchoalveolar portion was also observed. Significant increases in myeloperoxidase and interkeukin-6 levels were found in the high dose group.

Concentration and end point used for MRL derivation: The MRL is based on a minimal LOAEL of 0.5 ppm fluoride as hydrogen fluoride for upper respiratory tract irritation.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X]	3 for use of a minimal LOAEL
[ ]	3 for extrapolation from animals to humans with dosimetric adjustments
[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 concentration:

Was a conversion used from intermittent to continuous exposure? No. Data on nasal irritation from the Largent (1960) report, the Lund et al. (2002) study, and the intermediate-duration study by Largent (1960) provide suggestive evidence that the severity of nasal irritation does not increase with increasing exposure duration. These three studies identified similar LOAEL values for different exposure durations: 3.22 ppm 6 hours/day for 10 days (Largent 1960), 3.8 ppm 1 hour/day for 1 day (Lund et al. 2002), and 2.98 ppm 6 hours/day, 6 days/week for 15–50 days. Thus, time scaling was not used to derive the acute MRL.

Other additional studies or pertinent information that lend support to this MRL: The respiratory tract appears to be the primary target of hydrogen fluoride toxicity. Upper respiratory tract irritation and inflammation and lower respiratory tract inflammation have been observed in several human studies. Nasal irritation was reported by one subject exposed to 3.22 ppm fluoride as hydrogen fluoride 6 hours/day for 10 days (Largent 1960). Very mild to moderate upper respiratory symptoms were reported by healthy men exposed to 0.5 ppm fluoride as hydrogen fluoride for 1 hour (Lund et al. 1997). At higher concentrations, 4.2–4.5 ppm fluoride as hydrogen fluoride for 1 hour, more severe symptoms of upper respiratory irritation were noted (Lund et al. 1997, 2002). In subjects exposed to 4.2 ppm for 1 hour, analysis of nasal lavage fluid provided suggestive evidence that hydrogen fluoride induces an inflammatory response in the nasal cavity (Lund et al. 2002). Similarly, bronchoalveolar lavage fluid analysis revealed suggestive evidence of bronchial inflammation in another study of subjects exposed to 1.9 ppm fluoride as hydrogen fluoride for 1 hour (Lund et al. 1999); no alterations were observed at 0.5 ppm. Respiratory effects have also been reported in rats acutely exposed to hydrogen fluoride. Mild nasal irritation was observed during 60-minute exposure to 120 ppm fluoride (Rosenholtz et al. 1963), and respiratory distress was observed at 2,310, 1,339, 1,308, and 465 ppm fluoride for 5, 15, 30, or 60 minutes, respectively (Rosenholtz et al. 1963). Midtracheal necrosis was reported in rats exposed to 902 or 1,509 ppm fluoride as hydrogen fluoride for 2 or 10 minutes using a mouth breathing model with a tracheal cannula (Dalbey et al. 1998a, 1998b). These effects were not observed when the tracheal cannula was not used.

The Lund et al. (1997, 1999) study was selected as the basis of the acute-duration inhalation MRL for hydrogen fluoride. As reported in the 1997 publication, a trend (p=0.06) toward increased upper respiratory tract symptom score, as compared to pre-exposure symptom scores, was observed at the lowest concentration tested (0.5 ppm). A significant increase in the total symptom score was also observed at this concentration. No significant alterations in symptom scores were observed at the mid concentration (1.9 ppm), and increases in upper respiratory and total symptom scores were observed at the high concentration (4.5 ppm). Suggestive evidence of bronchial inflammation was also observed at ≥1.9 ppm fluoride (Lund et al. 1999), although no alterations in lower respiratory tract symptoms (Lund et al. 1997) or lung function (Lund et al. 1997) were observed at any of the tested concentrations.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name:	Fluorine
CAS Number:	7782-41-4
Date:	December 1, 2003
Profile Status:	Final
Route:	[X] Inhalation [ ] Oral
Duration:	[X] Acute [ ] Intermediate [ ] Chronic
Key to Figure:	6
Species:	Humans

Minimal Risk Level: 0.01 [ ] mg/kg/day [X] ppm

Reference: Keplinger ML, Suissa LW. 1968. Toxicity of fluorine short-term inhalation. Am Ind Hyg Assoc J 29(1):10-18.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Five volunteers (aged 19–50 years; gender not specified) were exposed to various concentrations of fluorine: 10 ppm for 3, 5, or 15 minutes; 23 ppm for 5 minutes, 50 ppm for 3 minutes, 67 ppm for 1 minute, 78 ppm for 1 minute, and 100 ppm for 0.5 or 1 minute. The fluorine was administered via a mask that covered the eyes and nose; the subjects could remove the mask from their face and could breathe fresh air via their mouth. No information was provided on the amount of time between exposures or whether all subjects were exposed to all concentrations.

Effects noted in study and corresponding concentrations: No nasal or eye irritation was noted by subjects exposed to 10 ppm for 3, 5, or 15 minutes; it was also noted that the 15-minute exposure did not result in respiratory tract irritation. Eye irritation was observed at ≥23 ppm; nose irritation at ≥50 ppm, and skin irritation at ≥78 ppm. The severity of the irritation was concentration related. Exposure to 100 ppm was considered very irritating and the subjects did not inhale during the exposure period. No incidence data were reported.

Concentration and end point used for MRL derivation: The MRL is based on a NOAEL of 10 ppm and LOAEL of 23 ppm fluorine for irritation in humans.

[X] NOAEL [] LOAEL

Uncertainty Factors used in MRL derivation:

- [ ] 10 for use of a LOAEL
- [ ] 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 concentration: NA

Was a conversion used from intermittent to continuous exposure? Yes. The 15-minute exposure duration was adjusted for a continuous 24-hour exposure using the following equation:

$$10 \text{ ppm} \times 0.25 \text{ hours}/24 \text{ hours} = 0.1 \text{ ppm}$$

The study authors noted that exposure to 10 ppm for 3–5 minutes every 15 minutes over a 2- or 3-day period resulted slight irritation to the eyes and skin, but no other subjective effects (no additional details on this study were provided). These data are suggestive that the toxicity of fluorine may be dependent on concentration and duration of exposure. Thus, it is appropriate to adjust for continuous exposure.

Other additional studies or pertinent information that lend support to this MRL: Respiratory effects have also been observed in, rats, mice, guinea pigs, rabbits, and dogs exposed to fluorine for 1–60 minutes (Keplinger and Suissa 1968). The observed effects include diffuse lung congestion, dyspnea, irritation, and alveolar necrosis and hemorrhage. The severity of the lung congestion was concentration-related and no species differences were found.

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

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

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

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

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

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

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

LEGEND

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

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data 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 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 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/day, 5 days/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, 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 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 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

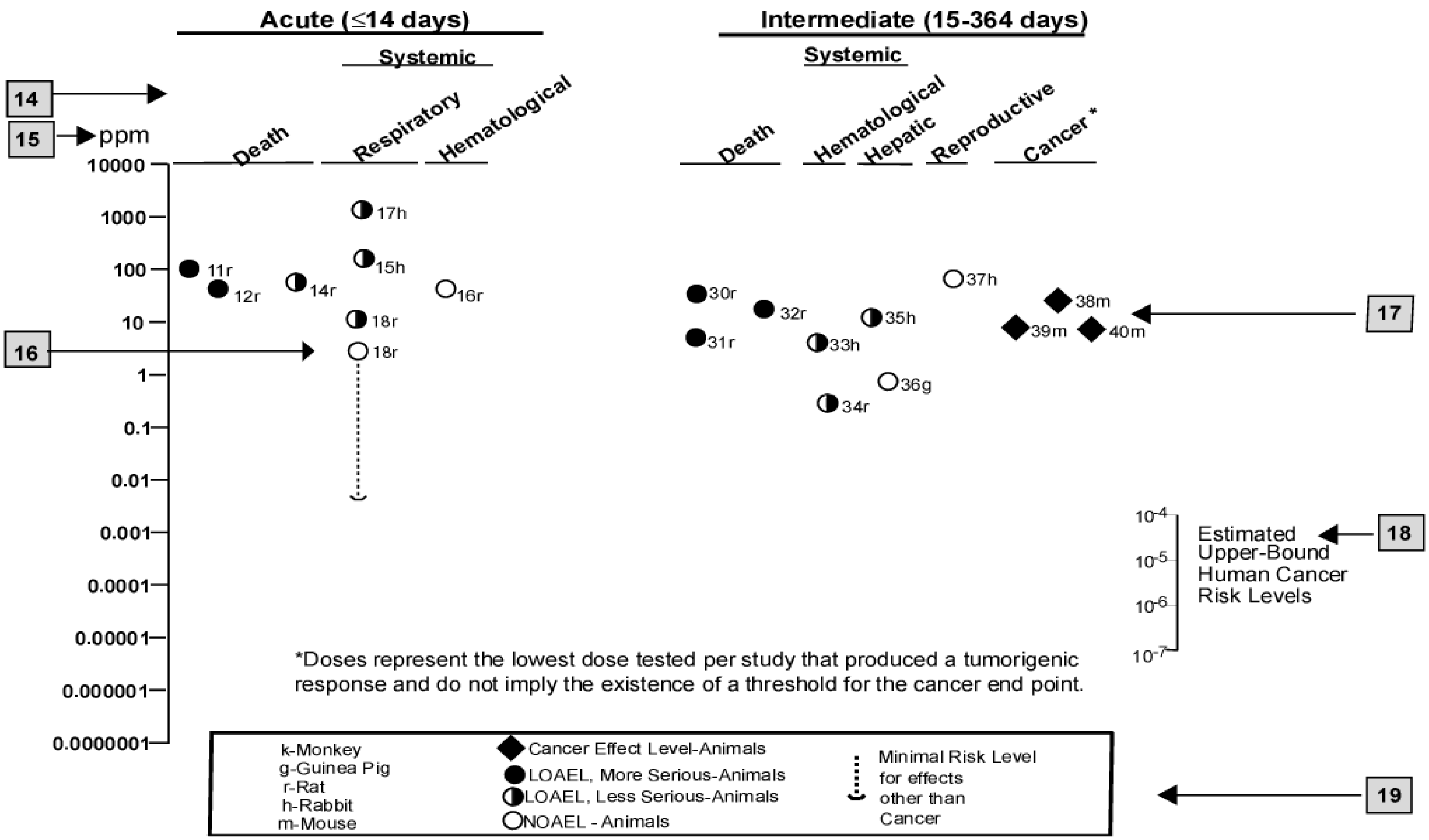
						LOAEL (effect)		
	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE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



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

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/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_{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
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

APPENDIX D. FLUORIDE AND DENTAL CARIES

Dental caries or tooth decay is a progressively destructive disease of the tooth caused by cariogenic bacteria. These bacteria, which reside in dental plaque, colonize on tooth surfaces and produce polysaccharides that enhance adherence of the plaque to the tooth enamel. Once plaque is formed, the bacteria on the teeth produce an enzyme that promotes erosion of the enamel by converting sugars and other fermentable carbohydrates into acids. The acids dissolve the minerals (calcium and phosphorus) in the tooth enamel in a process known as demineralization (DHHS 2001b).

Several studies conducted by Dean and associates in the 1930s and 1940s demonstrated a relationship between the levels of naturally-occurring fluoride in drinking water and the prevalence of dental caries (Dean 1938; Dean et al. 1939, 1941, 1942). Children living in communities with high levels of fluoride in the drinking water had lower occurrences of dental caries. This relationship between fluoride and dental caries prompted the city of Grand Rapids, Michigan to implement a water fluoridation program in 1945. Studies conducted in some of the earliest cities to adopt a fluoridation program reported dramatic decreases in the occurrence of dental caries (Ast et al. 1951; Dean et al. 1950; Hill et al. 1951; Hutton et al. 1951). The prevalence of dental caries in children living in communities with fluoridated water was 50–70% lower than in children living in areas without fluoridated water. Surveys conducted after the late 1980s found smaller differences; the occurrence of dental caries was 9–25% lower in communities with fluoridated water as compared to communities without fluoridated water (Brunelle and Carlos 1990; DeLiefde 1998; Eklund et al. 1987; Englander and DePaola 1979; Jackson et al. 1995; Selwitz et al. 1995). In one study, no significant differences in the occurrence of dental caries was found in school-aged children 5–17 years old (Yiamouyiannis 1990); however, when just 5 year olds were examined, the incidence of dental caries was 42% lower in children with lifetime exposure to fluoridated water and 24% lower in children exposed to fluoridated water for only a portion of their lifetime. Several studies have also examined the impact of termination of a water fluoridation program on the incidence of dental caries. Conflicting results have been reported. Some studies found increases in dental caries occurrence (Attwood and Blinkhorn 1991; Stephen et al. 1987; Thomas et al. 1995), some found no change in the occurrence of dental caries (Burt et al. 2000; Kalsbeek et al. 1993; Künzel and Fischer 1997; Seppä et al. 2000; Stephen et al. 1987), and other studies found decreases in dental caries occurrence (Künzel and Fischer 2000; Künzel et al. 2000; Maupomé et al. 2001). A meta-analysis of 26 studies examined the relationship between water fluoridation and prevalence of dental caries or the change in decayed, missing, and filled teeth (DMFT) (McDonagh et al. 2000). In 19 of the 30 analyses conducted, a significant increase in the prevalence of children without dental caries was found in the fluoridated areas compared to non-fluoridated areas. Additionally, 15 of the 16 analyses found a significant increase in the mean change in DMFT in fluoridated water areas (levels of DMFT declined in response to fluoridation).

The decline or stabilization of the occurrence of dental caries in the absence of water fluoridation has been attributed to a number of factors (Horowitz 1996), including diffusion of effects of fluoridated drinking water, dilution effects from other sources of fluoride on the measurement of effectiveness of community water fluoridation, and improved dental care. The diffusion effect occurs when residents of communities without fluoridated water consume products manufactured or bottled in areas with fluoridated water (thus fluoride enters the foodstuff) or attend schools in areas with fluoridated water. An often cited example of the diffusion effect is the 1986–1987 NIDR survey of dental health status of U.S. school children (Brunelle and Carlos 1990). In the Pacific region, which has a low percentage of communities with fluoridated water (19%), children living in area with nonfluoridated water have 61% higher dental caries score as compared to children living in areas with fluoridated water. In contrast, in the Midwest region with a high percentage of communities with fluoridated water (74%), there is no difference in dental caries scores between fluoridated and nonfluoridated areas. The dilution effect is due to the development and use of other fluoride agents, including fluoride supplements, fluoride solutions, gels, and varnishes used by dental professionals, fluoridated toothpaste, and fluoride mouthwash. The use of the fluoride products that provide protection from dental decay diminishes the difference in the levels of dental decay between fluoridated and nonfluoridated communities (Ripa 1993).

The primary mechanism by which fluoride prevents the occurrence of dental caries is through its influence on the demineralization and remineralization process (Featherstone 1999; Koulourides 1990; Ten Cate 1999). The acid produced from the metabolism of sugars and fermentable carbohydrates by cariogenic bacteria in plaque begins to dissolve or demineralize the enamel crystal surface of the tooth resulting in the loss of calcium, phosphate, and carbonate from the tooth enamel. The increased acid production results in a decrease in plaque pH and the release of fluoride from the dental plaque. This fluoride, along with calcium and phosphate, is incorporated into the apatite molecule to form fluor(hydroxyl)apatite. In the presence of fluoride, cycles of partial demineralization and then remineralization will create apatite, which has less carbonate, more fluoride, and is less soluble. Fluor(hydroxyl)apatite, which has high levels of fluoride and low levels of carbonate, is more acid resistant (Chow 1990; Ericsson 1977; Featherstone 1999; Kidd et al. 1980; Ten Cate 1999; Thylstrup 1990; Thylstrup et al. 1979). When the beneficial effects of fluoride on caries prevention was first discovered, it was believed that the incorporation of the fluoride into developing enamel resulted in improved enamel and dental caries prevention (Dean et al. 1935; McClure and Likins 1951). However, more recent data suggest that fluoride works primarily after teeth have erupted (Clarkson et al. 1996). In a fluoride-rich environment, demineralization and remineralization cycling, which occurs throughout the lifetime of the tooth, will result in teeth that are more resistant to cariogenic bacterial damage. Another mechanism in which fluoride prevents dental caries is via a direct effect on cariogenic bacterial metabolism. There are *in vitro* data that demonstrate that fluoride can inhibit bacterial metabolism of carbohydrates, which results in a decreased production of acids (Bowden 1990; Bowden et al. 1982; Marquis 1990; Rosen et al. 1978). However, it is likely that this would occur at fluoride levels that far exceed those present in the mouth (Geddes and Bowen 1990).

Based on this relationship between fluoride and dental caries prevention, the Institute of Medicine (IOM 1997) and the World Health Organization (WHO 2002) consider fluoride to be an essential dietary element. The Institute of Medicine has derived adequate intake levels (AIs) ranging from 0.01 to 4 mg/day (IOM 1997). The AIs for each age group are presented below:

Age Range	Adequate Intake Level (mg/day)
0–6 months	0.01
6–12 months	0.5
1–3 years	0.7
4–8 years	1
9–13 years (males and females)	2
14–18 years (males and females)	3
>18 years (males)	4
>18 years (females)	3

Expert panels convened by the U.S. Department of Health and Human Services (DHHS 1991, 2000, 2001b) and the World Health Organization (WHO 1994) support optimal fluoridation of drinking water. A work group assembled by the Centers for Disease Control and Prevention (DHHS 2001b) made the following recommendation:

> "Because frequent exposure to small amounts of fluoride each day will best reduce the risk for dental caries in all age groups, the work group recommends that all persons drink water with an optimal fluoride concentration and brush their teeth twice daily with fluoride toothpaste. For persons at high risk of dental caries, additional fluoride measures might be needed. Measured use of fluoride modalities is particularly appropriate during the time of anterior tooth enamel development (i.e., age <6 years)."