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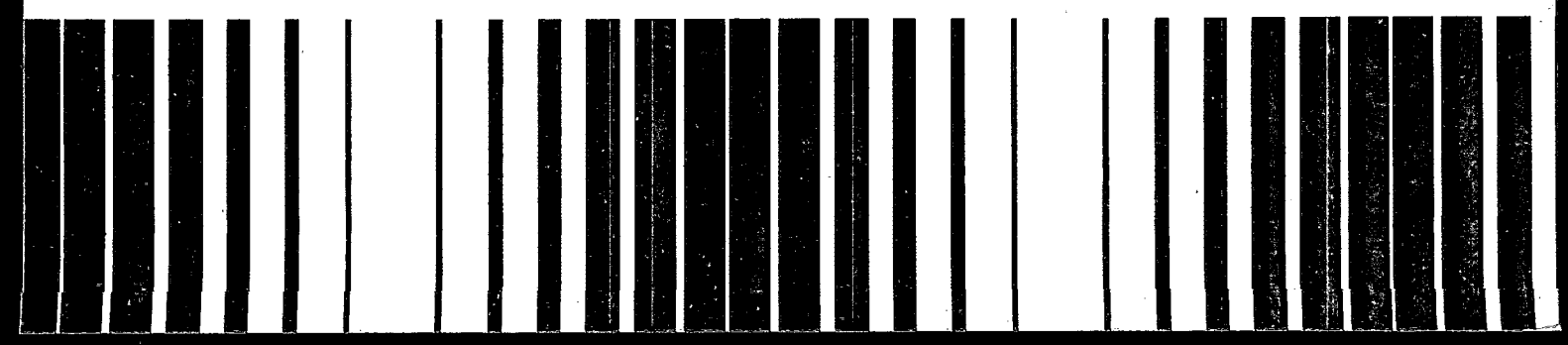
Seminar Publication

Risk Assessment, Management and Communication of Drinking Water Contamination



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Risk Assessment, Management and Communication of Drinking Water Contamination

Office of Drinking Water
Office of Water
U. S. Environmental Protection Agency
Washington, DC

Office of Technology Transfer and Regulatory Support
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U.S. Environmental Protection Agency
Cincinnati, OH 45268

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Acknowledgments

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Chapter 1

Introduction

1.1 About This Publication

Every week the news media bombard us with reports of toxic wastes threatening our environment, especially our drinking water supplies. In recent years a whole new group of manmade drinking water contaminants has emerged. Over 60,000 potentially harmful chemicals are now being used by various segments of U.S. industry and agriculture. These substances range from industrial solvents and pesticides to cleaning preparations and septic tank degreasers. When used or discarded improperly, these chemicals can pollute ground and surface waters used as sources of drinking water. Subsurface activities can also cause problems. Mining operations, the injection of waste chemicals and brines, and the storage of substances in underground tanks have all been linked to the contamination of ground and surface water. Not all problems of drinking water quality originate with the surface or ground-water supplies. Sometimes contamination can occur during the treatment process itself. In other cases it can occur while the water is in transit from the treatment plant to your home.

This publication was largely developed from the speakers' handouts for a series of EPA workshops entitled "Assessment and Management of Drinking Water Contamination." These workshops were designed for those involved in the management of drinking water contamination incidents – for example, local and state officials, consultants, and utility employees.

Each workshop attendee partici-pated in a hands-on case-study exercise for specific chemicals of concern (aldicarb, TCE, and vinyl chloride) for both a risk assessment and risk manage-ment problem. Of the approximately 125 people who attended each workshop, 28 percent were from state agencies (health and treatment technology), 28 percent were from city and county agencies and utilities, 13 percent were from federal agencies, 18 percent were consultants, and 13 percent were private or industrial water supply personnel.

1.2 Purpose and Scope

This publication discusses how to identify, assess, and manage the occurrence of potentially toxic chemicals in drinking water. It presents a broad range of information from the fields of toxicology, chemistry, and engineering, and is intended to assist the reader in assessing and managing drinking water contamination problems in his/her region, state, or locality.

Technical information is presented on U.S. EPA programs, toxicology, chemistry, treatment principles, and media coverage and risk communication during an emergency. In addition, exercises are included on particular risk assessment and management problems that center around specific EPA-ODW Health Advisory chemicals.

1.3 Organization of This Publication

This publication consists of six chapters and three appendices. It progresses through the essential steps in solving a drinking water contamination problem: review of available standards and advisories, assessment of risk, review of toxicology, review of risk reduction options, and risk communication.

Chapter 2 discusses the development of standards and health advisories, in addition to giving an update on the regulatory process for the provision of safe drinking water.

Chapter 3 goes through the various steps involved in performing a risk assessment: hazard identification, dose-response evaluation, human exposure evaluation, and risk characterization. Chapter 4 then describes the principles of toxicology, including

absorption, distribution, excretion, and metabolism. The toxicology of selected substances is also described.

Chapter 5 reviews the various risk reduction technologies available for removal of inorganic and organic contaminants. Where possible, the processes are described, equipment needed is presented, key design factors are noted, typical performance data are noted, and operation and maintenance data and costs are given. Comparative technology tables appear in this chapter.

Chapter 6 covers the management of media coverage and communication with the public.

This publication contains three appendices. The first provides the current (1989) drinking water standards. The second contains examples of the latest health advisories for aldicarb, atrazine, trichloroethylene, and vinyl chloride. The third appendix contains example exercises for risk assessment and risk management/reduction.

Chapter 2

Development of Drinking Water Regulations and Health Advisories by EPA's Office of Drinking Water

2.1 Background for Promulgation of Standards Under the Safe Drinking Water Act and Amendments

2.1.1 Safe Drinking Water Act

The Safe Drinking Water Act of 1974 (SDWA) directed the U.S. Environmental Protection Agency to identify and regulate substances in drinking water that, in the judgment of the Administrator, may have an adverse effect on public health (1). It included interim regulations (National Interim Primary Drinking Water Regulations - NIPDWRs) to be established within 180 days of enactment of the SDWA and National Primary Drinking Water Regulations (NPDWRs) to be finalized over a period of years, with the amendments promulgated in 1986. The National Drinking Water Regulations were subdivided into primary regulations, affecting public health, and secondary regulations, affecting aesthetic qualities relating to the public acceptance of drinking water.

The most relevant criteria for this selection of contaminants for regulation are the potential health risks and the occurrence or potential occurrence in the drinking water (2). For each of the substances or contaminants that the EPA identifies, there are two methods for developing regulatory measures. The EPA must either establish a Maximum Contaminant Level (MCL) or, if it is not economically or technically feasible to monitor the contaminant level in the drinking water, specify a treatment technique to remove the contaminant from the water supply or reduce its concentration in the water supply.

The standards development process involves an intensive technological evaluation that includes many factors: occurrence in the environment; human exposure in specific and general populations; health effects; analytical methods of detection; chemical transformations of the contaminant in the drinking water; and calculations of population risks of adverse health effects, treatment technology, and costs.

The NPDWRs follow specific steps for promulgation (see Figure 2-1). EPA first publishes a proposed Drinking Water Priority List (DWPL) of contaminants for future regulation. Then the Agency accepts public comment, publishes a final DWPL, publishes proposed regulations and accepts public comment, and finally publishes final regulations.

The SDWA Amendments mandate that EPA propose the MCLs, which are enforceable standards, and Maximum Contaminant Level Goals (MCLGs), which are nonenforceable health goals, simultaneously (3). For each contaminant, MCLG development occurs first; and then the MCL is set as close to the MCLG as is feasible, taking into consideration analytical methods, treatment technology, economic impact (costs), and regulatory impact (see Figure 2-2).

2.1.2 Standards Development for Noncarcinogens

For noncarcinogens, MCLGs are derived in the three-step process described in Table 2-1. The first step is calculating the Reference Dose (RfD; formerly called Acceptable Daily Intake, or ADI) for each specific contaminant. The RfD is an estimate of the amount of a chemical that a person can be exposed to on a daily basis that is not anticipated to cause adverse systemic health effects over the person's lifetime. The RfD is usually given in milligrams of chemical per kilogram of body weight per day (mg/kg/day), has an overall built-in uncertainty spanning perhaps an

Figure 2-1. Regulatory development process

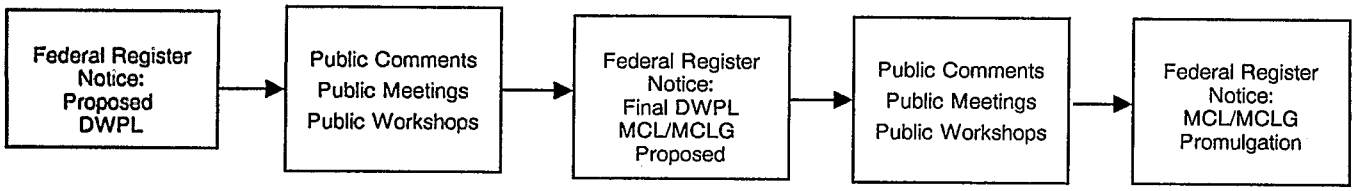


Figure 2-2. MCL/MCLG development

Risk Assessment	*Risk Assessment*
Hazard Identification	Risk Assessment
+	+
Dose-Response Assessment	Analytical Methods
+	+
Human Exposure Assessment	Technology and Costs
+	+
Risk Characterization	Economic and Regulatory Impact
↓	↓
MCLG (Health-Based Goal)	MCL (The Legal Limit)

order of magnitude, and takes into consideration sensitive human subgroups.

The RfD is derived from a No- or Lowest-Observed-Adverse-Effect Level (NOAEL or LOAEL), which is calculated on the basis of data from a subchronic or chronic scientific study of humans or animals. The NOAEL or LOAEL is divided by an uncertainty factor to obtain the RfD. The uncertainty factor takes into account intra- and interspecies diversity and sensitivities, limited or incomplete data, significance of the adverse effect, length of exposure, and pharmacokinetic factors. This uncertainty factor can range from 1 to 10,000.

From the RfD, a Drinking Water Equivalent Level (DWEL) is calculated by multiplying the RfD by an assumed body weight of 70 kg for an adult and then dividing by an average adult water consumption of 2 L per day. The DWEL assumes that 100 percent of exposure to a substance will be from drinking water.

The MCLG is determined by multiplying the DWEL by the percentage of the total daily exposure contributed by drinking water (relative source contribution), as seen in Table 2-1. For non-carcinogens, the MCLG will often equal the MCL. (When determ-ining the MCL/MCLG, generally, ODW rounds the final calculation to one significant figure.).

Table 2-1. Determining the MCLG

Determine RfD (Reference Dose) in mg/kg/day:

$$RfD = \frac{\text{NOAEL or LOAEL in mg/kg/day}}{\text{Uncertainty Factor}}$$

Determine DWEL (Drinking Water Equivalent Level) in mg/L assuming 100 percent drinking water relative source contribution (RSC) and adult weighing 70 kg:

$$DWEL = \frac{(RfD)\ (70\ kg)}{(2\ L/day)}$$

Determine MCLG in mg/L:

$$MCLG = (DWEL)\ (\text{Percent drinking water RSC})$$

Note: If actual exposure data are not available, ODW assumes an RSC of 20%. RSCs as high as 80% may be set for some contaminants when exposure data show large contributions from drinking water.

Preferred data for RfD and DWEL development (in order of preference under each subheading) are shown in Table 2-2.

Table 2-2. Preferred Data for RfD and DWEL Development

Duration of Exposure - Chronic - Subchronic	Dose-Response Relationship - NOAEL and LOAEL - LOAEL or NOAEL
Route of Exposure - Oral: drinking water, gavage, diet - Inhalation - Subcutaneous or intraperitoneal	End-point of Toxicity - Biochemical/pathophysiological changes - Body/organ weight changes - Mortality
Test Species - Human - Most sensitive species - Animal model	

2.1.3 Standards Development for Potential Carcinogens

A separate health assessment system is used for potentially "nonthreshold" no-effect-level chemicals with carcinogenic potential. Carcinogenicity is generally assumed to be a nonthreshold phenomenon, meaning that any exposure is assumed to represent some finite level of risk in the absence of sufficient negative information. Precedence was given to this method in the House Report that accompanied the SDWA of 1974, indicating that MCLGs for nonthreshold toxicants (i.e., carcinogens) should be set at zero (4).

If toxicological evidence leads to the classification of the contaminant as a human or probable human carcinogen, the MCLG is set at zero. Mathematical models are used to calculate drinking water concentrations associated with estimated excess cancer risk levels (e.g., 10^{-4}, 10^{-5}, 10^{-6}). A lifetime risk of 10^{-4}, for example, indicates a possibility of one additional case of cancer for every 10,000 people exposed over a 70-year lifetime; a risk of 10^{-5} indicates one additional cancer per 100,000 exposed individuals.

The data used in these risk estimates usually come from lifetime exposure studies in animals. To predict the risk for humans, these animal doses must be converted to equivalent human doses. This conversion includes correction for noncontinuous animal exposure, less than lifetime studies, and differences in animal/human surface area and weight. The size differential is assumed to be proportional to the difference in body surface area, which is approximated by the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg.

For contaminants with carcinogenic potential, drinking water concentrations are correlated with the carcinogenic risk estimates by employing a cancer potency (unit risk) value together with the assumption for lifetime exposure via ingestion of 2 L of water per day. The cancer unit risk is usually derived from a linearized multistage model with a 95 percent upper confidence limit providing a low-dose estimate. The true cancer risk to humans is not likely to exceed this upper limit estimate and, in fact, may be lower.

Excess cancer risk estimates may also be calculated using other models such as the one-hit, Weibull, logit, and probit models. (See Chapter 3, Section 3.3.2.2.) Given the current limited under-standing of the biological mechanisms involved in carcinogenesis, no one of these models can be said to predict risk more accurately than another. Each model is based on differing assumptions; thus, the estimates derived for the various models can differ by several orders of magnitude.

A number of uncertainties are associated with the scientific database used to calculate and support cancer risk estimates. For example, cancer studies are usually performed with experimental animals, and extrapolating these data to humans is difficult due to a lack of understanding of the biological mechanisms involved. Insufficient knowledge concerning the health effects of contaminants in drinking water; the impact of the experimental animal's age, sex and species; and the nature of the target organ system(s) examined adds uncertainty to the use of the database. Dose-response data are gathered in animals at high levels of exposure rather than at the lower levels typical of human exposure. Finally, most exposures are to more than one contaminant, and little is known regarding possible synergistic or antagonistic effects between mixture components. All of these uncertainties support use of the generally more conservative linearized multistage model for estimating cancer risk rates. Using one model also fosters a consistency of approach. However, some data suggest that other models, such as the one-hit, may be more appropriate than the linearized multistage model.

Several scientific groups have designed carcinogenic chemical classification schemes on the basis of weight of evidence for carcinogenicity, including the EPA, National Academy of Sciences (NAS) Safe Drinking Water Committee, and the International Agency for Research in Cancer (IARC) (5). Table 2-3 describes EPA's classification groups and Table 2-4 shows EPA's three-category approach for setting MCLGs (6).

Note that in Table 2-4 the MCLG for Category I chemicals is set at zero as an aspirational goal. The problem with setting the MCLG at zero is that a zero level is unattainable and is below the analytical detection level. MCLGs for Category II contaminants can be calculated with the reference dose (RfD) approach and an additional safety/uncertainty factor of 1-10. If adequate systemic data are not available to calculate an RfD, the MCLG may be represented by 10^{-5} to 10^{-6} excess cancer risk range. Category III adheres to the RfD approach to accommodate for the extrapolation of animal data to human risk, for the existence of weak or insufficient data, and for individual differences in human sensitivity to toxic agents. The general guidelines used to calculate the uncertainty factors are based on the NAS recommendations, and are shown in Table 2-5 (7).

The guidelines help in determining risk, but evaluating carcinogenic potential is controversial in light of the divergent interpretations of the scientific community.

Table 2-3. EPA Carcinogenic Assessment Categories

A.	Human carcinogen, based on sufficient evidence from epidemiological studies
B.	Probable human carcinogen, based on at least limited evidence of carcinogenicity to humans (B1), or usually a combination of sufficient evidence in animals and inadequate data in humans (B2)
C.	Possible human carcinogen, based on limited or equivocal evidence of carcinogenicity in animals in the absence of human data
D.	Not classifiable, based on inadequate evidence of carcinogenicity from animal data
E.	No evidence of carcinogenicity for humans (no evidence of carcinogenicity in at least two adequate animal tests in different species or in both epidemiological and animal studies)

Table 2-4. EPA's Three-Category Approach

Category	Evidence of Carcinogenicity	Class	MCLG Setting Approach
I	Sufficient evidence in humans or animals	EPA Group A or B; IARC 1, 2A, 2B	0
II	Limited or equivocal evidence in animals	EPA Group C	1) RfD approach with additional safety factor 2) 10^{-5} to 10^{-6} cancer risk range
III	Inadequate or negative evidence from animal data	EPA Group D or E; IARC 3, 4	RfD approach

Table 2-5. Guidelines on the Use of Uncertainty Factors

Uncertainty Factor	Guideline
1-10	When a NOAEL from a human study is used (to account for intraspecies diversity)
100	When a LOAEL from a human study is used, incorporating a factor of 10 to account for lack of a NOAEL and a factor of 10 for intraspecies diversity; or, when a NOAEL from an animal study is used, incorporating a factor of 10 to account for interspecies diversity and a factor of 10 for intraspecies diversity
1,000	When a LOAEL from an animal study is used, incorporating factors of 10 each for lack of NOAEL, interspecies diversity, and intraspecies diversity
1-10	Additional uncertainty factors, ranging from 1 to 10, may be incorporated on a case-by-case basis to account for deficiencies in the database

2.1.4 Analytical Methods

In addition to criteria for health risk, EPA must specify the analytical method best suited to detecting the amount of a contaminant in drinking water. Setting an MCL or MCLG for a chemical below the smallest amount detectable is not feasible. Thus, for each MCL or MCLG it derives, the Agency must specify an analytical method to be used, such as purge and trap gas, high performance liquid chromatography, mass spectrometry, and photoionization.

2.1.5 Feasibility and Best Available Technology (BAT)

The SDWA Amendment directs EPA to set MCLs as close to MCLGs as "feasible." "Feasible" means as close as possible "with the use of best technology, treatment techniques, or other means which the Administrator finds are available (taking cost into consideration) after examination for efficacy under field conditions and not solely under laboratory conditions" (8). Determining the feasibility of controlling a contaminant requires an evaluation of several factors:

After each HA has been prepared and becomes available for public use, it is entered into a computer-based HA Registry, and executive summaries for quick reference are entered into the Integrated Risk Information System (IRIS), an electronic database for information on risk assessment and risk management throughout EPA. IRIS is available to the public and EPA staff through the B.T. Tymnet Electronic Mail Network and National Library of Medicine's Toxnet.

Developing an HA is a step-by-step process estimated to require approximately 18 months from the time of identification of the chemical to issuance of a final document. The development process includes a minimum of four separate review steps by individuals within and outside of EPA to ensure quality and accuracy. After in-house review, a draft HA is submitted to an external peer review panel of recognized experts as well as to an Agency-wide review before the final draft HA is prepared. This final draft is then presented for public comment. A final HA is not issued for public use until all phases of the review process have been satisfied.

2.5.1 Legal Status of Health Advisories

Health Advisories are neither legally enforceable standards nor are they issued as official regulations. They may or may not lead to the issuance of MCLs. The HAs do not condone the presence of contaminants in drinking water; rather, they are prepared to provide specific advice on the levels of contaminants as they relate to possible health effects. They describe, rather than prescribe, concentrations of contaminants in drinking water at which adverse noncarcinogenic effects are not anticipated to occur following one-day, ten-day, longer-term, or lifetime exposures. The HAs are subject to change and are updated as new and better information becomes available.

2.5.2 Content of Health Advisories

Health Advisories present, in a capsular or "bullet" format, essential background information for developing a concise, but complete, profile of a chemical. The standard format for HAs is outlined in Table 2-14.

Following a brief standard introduction explaining the HA program, general information and properties of the specific chemical are presented. To assist in chemical identification, the physical and chemical properties are given in table format along with the various synonyms and uses. Occurrence and environmental fate data are included as a means of determining the extent of possible human exposure. All available information on the pharmacokinetic properties of the chemical are included, with particular emphasis on the chemical's absorptive properties and known metabolites. When data are available on health effects in humans, all pertinent details are reported, including dose and mode of exposure and the effects resulting from acute and chronic exposures.

Table 2-14. ODW Health Advisory Content

I. General Introduction

II. General Information and Properties
- --Synonyms --Uses --Properties
- --Occurrence --Environmental Fate

III. Pharmacokinetics
- --Absorption --Distribution
- --Metabolism --Excretion

IV. Health Effects
- Humans Animals
- - Short-Term Exposure
- - Dermal/Ocular Effects
- - Long-Term Exposure
- Developmental/Reproductive/Mutagenic/Carcinogenic Effects

V. Quantification of Toxicological Effects
- --One-Day Health Advisory --Ten-Day Health Advisory
- --Longer-Term Health Advisory --Lifetime Health Advisory
- --Evaluation of Carcinogenic Potential

VI. Other Criteria, Guidance, and Standards

VII. Analytical Methods

VIII. Treatment Technologies

IX. References

Since the bulk of information on the toxic effects of chemicals is usually derived from animal studies, Section IV of an HA is often the most comprehensive. If available, the animal data will include both short-term and long-term exposure studies, reproductive and developmental effects, and mutagenicity and carcinogenicity data, as well as any available dermal and ocular effects information. However, since an HA is intended to be a brief guidance document, only those studies deemed most pertinent to its presence as a contaminant in drinking water are included. Thus, the HA is not meant to review all available data but rather only the best data available on the specific chemical.

Section V, Quantification of Toxicological Effects, presents the rationale used in selecting the studies for development of the one-day, ten-day, longer-term, and lifetime HA exposure values. These expo-sure values are developed from data describing only noncarcinogenic endpoints of toxicity. If a chemical is a known or probable human carcinogen, the HA document includes carcinogenic potency factors and drinking water concentrations that are estimated to represent excess lifetime cancer risks.

consensus for risk assessment procedures for estimating human risk levels via dermal exposure (i.e., washing, bathing, etc.) from drinking water contaminants. Dermal dose-response data for most contaminants are lacking, especially for exposures and toxic endpoints outside the occupational setting. Whether effects from dermal exposures are significant relative to other exposures is often debatable, but the lack of data prevents resolution of the issue for many contaminants.

ODW's extensive research needs transcend the needs of other EPA offices (air, hazardous waste, toxic substances, etc.), as well as of other regulatory and health agencies at the federal, state, and local level. While EPA has some limited research funding capabilities, many of ODW's toxicity data needs must be met by research supported by other private or public sector sponsors. Where modest adjustments can be made in toxicity study protocols to meet multiple needs, innovative and cooperative funding arrangements should be sought to support research. Regardless of how individual research projects are funded, ODW requests that consideration always be given to no-cost or low-cost adjustments to testing protocols that extend the utility of the results to better meet ODW's needs.

Thus, the primary focus of future toxicological and epidemiological research undertaken for EPA must be to provide the essential quantitative dose-response data needed to support policymaking and regulatory decisions required under the SDWA Amendments. Research efforts should be directed toward the identification of the significant toxic endpoints and the quantification of the dose-response relationships needed to develop MCLGs.

2.5 Health Advisory Program Administered by the Office of Drinking Water

In addition to regulating drinking water contamination, ODW provides nonregulatory guidance on drinking water contamination through its Health Advisory program. The Health Advisory (HA) program provides documents on specific chemicals being regulated or monitored for possible regulation. The HA documents include information on health effects, analytical methodologies, and treatment technologies for assessing and managing contaminated drinking water. HAs specify nonregulatory concentrations of contaminants in drinking water at which adverse health effects are not anticipated to occur over specific durations of exposure. These numbers are derived from various human and animal studies that are discussed in the HA documents. A margin of safety is included in the HA values to protect sensitive members of the observed population. The HA values are not legally enforceable federal standards but instead provide informal technical guidance for federal, state, and local health officials. The HA documents also discuss analytical methods proven to be acceptable and treatment methods used or under consideration.

The HA exposure values are developed from appropriate short- or long-term data describing noncarcinogenic endpoints of toxicity. For all chemicals with sufficient data, one-day, ten-day, and longer-term HAs are derived, with accompanying explanations.

Health Advisories for lifetime exposures are not calculated for human or probable human carcinogens. Rather, projected excess lifetime cancer risks (unit risk) are provided to estimate the concentrations of the contaminant that may pose a carcinogenic risk to humans. These hypothetical estimates are usually presented as upper 95 percent confidence limits derived from the EPA linearized multistage model of risk extrapolation and are considered unlikely to underestimate the actual cancer risk. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit, and probit models. Since these models are based on different assumptions, the resulting risk estimates may differ by several orders of magnitude. These models are explained more fully in Chapter 3, Section 3.3.2.2.

When a draft Criteria Document (CD) (see Section 2.4) has been drafted by ODW, the HA is based on this document. Individuals desiring further information on the toxicological database or rationale for risk characterization should consult the CD. Criteria Documents and HAs are available for review at each EPA regional office or Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch) or, for a fee, from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161.

The HA program, as conducted by ODW, is an ongoing, multifaceted program designed to provide the most currently available information on potential or known drinking water contaminants as soon as such information is needed (i.e., in response to contamination incidents). Earlier phases of the program, which began in 1979, have resulted in the preparation of HAs for approximately 50 drinking water contaminants. Currently, HAs for approximately 60 pesticides have been finalized. HAs for 20 unregulated volatile organic chemicals (VOCs) and 30 inorganics, disinfectants, and disinfection by-products are in the process of preparation. The Department of the Army has also entered into a cooperative program with the EPA to develop HAs for various munitions chemicals that can contaminate drinking water.

6) Other Criteria, Guidance and Standards, 7) Analytical Methods, 8) Treatment Technologies, and 9) References.

2.4.2 Quantification of Toxicological Effects

The fifth chapter of the CD, covering quantification of toxicological effects (QTE), integrates key health effects information and provides the basis for the proposed MCLG. Risk assessments described in this section are designed to define the level at which no known or anticipated adverse effects on human health may occur while allowing for an adequate margin of safety to protect more sensitive individuals. The QTE for a chemical consists of separate assessments of noncarcinogenic and carcinogenic health effects. Chemicals that do not produce carcino-genic effects are believed to have a threshold dose below which no adverse noncarcinogenic health effects occur. Carcinogens are assumed to act without a threshold (i.e., there is no exposure level that is assumed to be without some level of health risk). For nonchemical drinking water contaminants (e.g., microorganisms), the organizational structure and risk assessment procedures are modified, as required by the contaminant's health effects properties. These case-by-case exceptions to the QTE's structure, however, are not addressed here.

2.4.3 Noncarcinogenic Effects

In the quantification of noncarcinogenic effects, a Reference Dose (RfD) (formerly termed the Acceptable Daily Intake - ADI), is calculated. The RfD is an estimate (with an uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious health effects during a lifetime of exposure. To calculate the RFD, see Section 2.1.

2.4.4 Carcinogenic Effects

Carcinogenic effects are quantified as described in Section 2.1.3. Excess cancer risk estimates are produced from lifetime animal exposure data, epidemiological data, and mathematical models.

2.4.5 Development of MCLGs

Using the assembled information on noncarcinogenic and carcinogenic effects, ODW employs a three-category approach to develop the MCLG for each contaminant. This approach is summarized in Table 2-4 and Section 2.1.3.

2.4.6 Research Needs For Developing Regulation

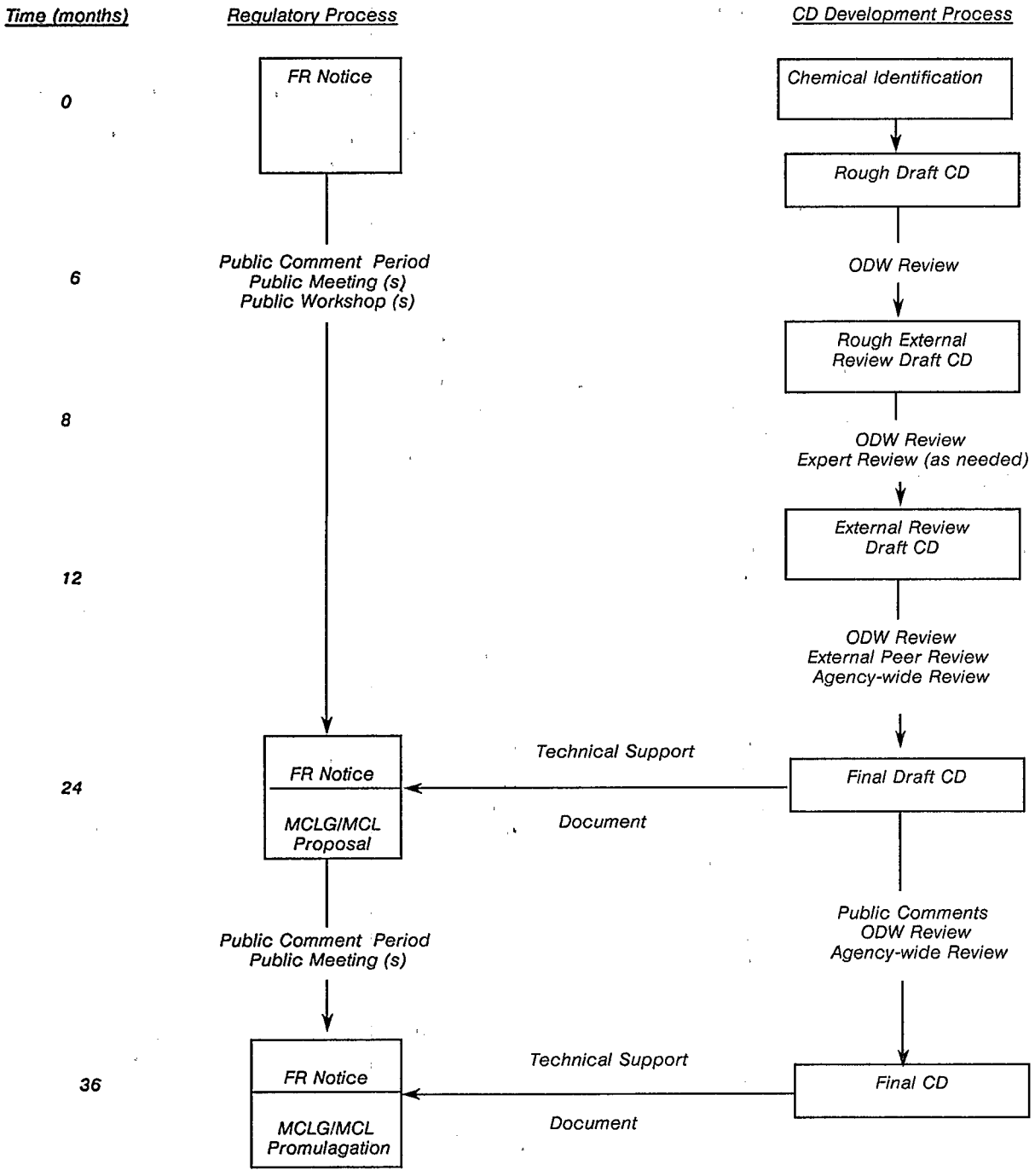
ODW is conducting the most detailed and comprehensive assessment of drinking water quality specifications ever attempted. These efforts are hampered by the lack of quantitative dose-response information on noncarcinogenic and carcinogenic effects for several of the contaminants to be regulated. As a result, Drinking Water CDs are left incomplete and attempts are thwarted to derive meaningful drinking water standards. Of particular concern are evalu-ations of the carcinogenic potential of contaminants. The SDWA requires that a finding of carcinogenicity (no safe threshold) for a particular contaminant leads to a MCLG set at zero. Such findings have widespread impact and must be validated to withstand the scientific and legal challenges encountered during the regulatory review process.

ODW's first priority in research is dose-response toxicity data from long-term, lifetime animal or human studies. Even when such data are available for a contaminant, however, duplicate data from the same and other species are highly desirable. Uncertainties associated with intra- and interspecies diversity often force ODW to adopt conservative risk assessment policies for deriving the MCLG values. The more comprehensive the database for a chemical, the greater the certainty in making risk extrapolations to humans. While ODW strives to estimate realistic, safe human exposure levels, the office must retain the "margin of safety" principle incorporated in the SDWA. This leads to criticisms and controversy that could be reduced by more comprehensive toxicity databases.

Major sources of uncertainty that are worthy of emphasis here are concerns over the most sensitive toxicity endpoint and most sensitive subpopula-tion(s). A drinking water standard should provide public health protection from all adverse effects. The heavy reliance on toxicity data from the open literature creates uncertainty as to whether the most sensitive toxicity endpoints have been evaluated. Toxicity research is usually focused within academic disciplines (e.g., neurotoxicity, development effects, renal effects), and does not evaluate other potentially relevant toxicity endpoints. Filling these information voids for drinking water contaminants, even with negative data, would provide added confidence during risk assessments. Similarly, comparative toxicity or pharmacokinetic studies that identify effects associated with different species, ages, gender, etc., are valuable in selecting the most appropriate human model and identifying the most sensitive subpopulations that require protection.

ODW also strongly supports research on a variety of scientific issues associated with performing risk assessments, including: 1) improving the use of pharmacokinetic information in evaluating dose-response data; 2) improving procedures for estimating human inhalation exposures due to contaminants in drinking water (i.e., relevant to showering, cooking, etc.); and 3) developing a

Figure 2-3 Criteria Document development process.



2.4.1 Major Elements of a Criteria Document

By definition, the EPA is required to promulgate NPDWRs for contaminants that are known or anticipated to occur in drinking water and that may cause an adverse human health effect. The primary objectives of CDs are, therefore, to establish core information based on health effects of chemicals in drinking water and to compile and evaluate data for providing the qualitative and quantitative health effects basis for MCLGs. Each CD consists of nine chapters : 1) Introduction, 2) General Information and Properties, 3) Pharmacokinetics, 4) Health Effects, 5) Quantification of Toxicological Effects,

Ozone: Ozone is used extensively in water treatment as a primary disinfectant. The use of this oxidant will probably increase in the U.S. as the study of chlorinated by-products continues. However, since ozone does not leave a residual oxidant in the water entering the distribution system, as chlorine does, its use can pose a problem in maintaining water quality. Regrowth of biological contaminants and decreased effectiveness of disinfection may occur as the water passes through the distribution system.

The mutagenic activity of ozone and its by-products in water has been assessed. Ozone was not reported to increase mutagenic activity in a number of bacterial systems (29).

2.3.6 MCLs/MCLGs by January 1991: 25 Additional Chemicals

The sixth phase of regulation will begin the first cycle of the Safe Drinking Water Act requirement to regulate or reassess 25 additional substances every 3 years. The regulatory effort will also include development of Drinking Water Priority Lists (DWPLs) to be published every 3 years.

Substances for future regulatory consideration include those chemicals listed pursuant to SDWA Section 1428 (wellhead protection), other CERCLA Section 101 substances, and substances not included on the first Drinking Water Priority List because of data limitations.

The first DWPL was proposed in July 1987 and finalized January 22, 1988. MCLs are required to be set for at least 25 substances from this list within 36 months of finalization. This process is scheduled to be repeated every three years. A number of organizations will be involved in identifying the best candidate substances from the DWPL to meet this schedule. These organizations include, within EPA for example, the program offices for Superfund and hazardous waste, ground water, water quality, pesticides, and toxic substances. In addition, EPA will consult with outside groups, such as the National Toxicology Program.

Since the lists of additional chemicals will include substances for which insufficient data are available, EPA must consider how to fill the data gaps on health effects, analytic methodology, occurrence, and treatment technologies for those substances. Researchers must look across the board at private wells, additive substances, surface waters, waste waters, environmental chemistry of substances, the mobility of these substances in the environment, and their mechanisms of entering drinking water (either in the ground or on the surface). Also requiring study are patterns of use of these compounds and their production, properties of biodegradation and absorption, and the amounts in which they are found.

These research needs could be used to set priorities across EPA programs and throughout the Agency, thus consolidating the decision-making processes of a variety of programs.

2.4 Criteria Documents

Drinking Water Criteria Documents (CDs) are being prepared for most contaminants to be regulated. These provide the health effects basis for establishing the MCLGs. Developing CDs requires evaluation of pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology, and mechanisms of toxicity. Emphasis is placed on data providing dose-response information. Thus, while the literature search and evaluation performed in support of each CD is comprehensive, only the reports considered most pertinent to the derivation of the MCLG are cited in the CDs.

Figure 2-3 illustrates the process used to develop a CD. During the first year of the process, the CD rough draft and rough external review draft are prepared. These drafts are presented to experts within EPA for review and comment on the adequacy of the database and risk assessments proposed as the health basis for the MCLG. Before preparing the final draft CD, EPA submits the external review draft to a panel of recognized experts outside the Agency for a thorough, critical review. Following this revision, the final draft CD serves as the technical support document covering health effects for the proposed MCLG published in the *Federal Register*. Inputs from the review and comment period on both the final draft CD and the proposed MCLG are considered in producing the final version of the CD. The final CD serves as the technical support document covering health effects for the final rule promulgating the MCLG.

During the regulatory process for a chemical, ODW prepares other documents dealing with analytical methods, treatment technologies, human exposure potential and cost-benefit analyses for that contaminant. These documents are used to derive the proposed and final MCL, which is set as close to the MCLG (i.e., health goal) as is feasible. Thus, by providing the health basis for deriving the MCLG, the CD serves as the keystone to the regulatory process for drinking water contaminants. The MCL is then derived from the MCLG by adjusting this health goal level to a level that can feasibly be attained, given the availability and cost of analytical methods and treatment technologies. If at any time during the CD and regulatory processes, new data show that the proposed MCLG and/or MCL are inadequate to protect human safety, these regulations may be amended. Additionally, the relevance and adequacy of the NPDWRs are to be reviewed at least every three years and revised regulations promulgated when appropriate.

more expensive to use than chlorine, chlorine dioxide is a good oxidizing agent and does not produce significant amounts of chlorine by-products. It does, however, produce milder oxidation products such as aldehydes.

Chlorine dioxide has also proven to be an effective disinfectant, with nearly 2.5 times the oxidizing power of chlorine. Chlorine dioxide degrades into chlorite (ClO_2^-) and, to a lesser extent, chlorate (ClO_3^-) during these processes.

The health effects of chlorine dioxide and its conversion products are primarily hematological, presumably due to its oxidizing nature.

The National Academy of Sciences (NAS) has calculated a Suggested-No-Adverse-Response Level (SNARL) of 0.3 mg/L for chlorine dioxide and 0.02 mg/L for chlorite and chlorate, assuming a 20 percent contribution from drinking water (22). However, since these substances are almost uniquely found in drinking water, the estimation of a 20 percent relative source contribution is probably low.

Chloramine: Chloramine is an alternative to chlorine for disinfecting drinking water. Chloramines are less reactive than chlorine and, due to their persistence, are best used as secondary residual maintenance disinfectants rather than primary pathogenic control agents. They do not treat resistant organisms, such as viruses and Giardia, as effectively as chlorine but are an inexpensive way of quenching the formation of halomethanes and other by-products. Chloramines also reduce unpleasant tastes and odors connected with the formation of chlorophenolic compounds. The primary toxic effect of chloramine in reported studies appears to be its hematological effects. Persons on hemodialysis may be at risk if chloramines are present in dialysate water.

Further research is necessary to determine chronic health effects. The NAS has estimated a SNARL of 0.5 mg/L for chloramines, assuming a 20 percent relative drinking water source contribution (21).

2.3.5.3 *Disinfection By-Products*

Trihalomethanes (THMs): Trihalomethanes regulated in drinking water include chloroform, bromoform, bromodichloromethane, and dibromochloromethane. These compounds are formed from the reaction of chlorine with organic matter in the water, such as humus, fulvic acids, and amides. Liver and kidney effects due to THM exposure have been observed in rats, mice, and dogs, as well as decreased immune system functions in mice (23, 24, 25).

The most noted health effect reported to result from exposure to THMs - and in particular chloroform - is carcinogenicity. Chloroform has been found to be carcinogenic in rats and mice. The National Cancer Institute reported an increased incidence of kidney tumors in male rats and liver tumors in male and female mice when chloroform was administered by gavage in a corn oil vehicle (26). Kidney tumors were also reported in male rats exposed to chloroform in drinking water (27) and male mice exposed to chloroform in toothpaste (28). Liver tumors were not reported to be significantly increased in the drinking water or toothpaste studies. While chloroform has been implicated in bladder, colon, and rectal cancers in humans, the evidence is inconclusive.

The EPA currently has set an MCL of 0.10 mg/L for total trihalomethanes. According to the NAS report, this limit corresponds to an upper-bound incremental lifetime cancer risk on the order of 1 in 100,000 (i.e., 10^{-5}) (22). This MCL, based primarily on treatment capabilities, was established as an interim National Primary Drinking Water Regulation and is under reevaluation.

Chlorinated Acids, Alcohols, Aldehydes, and Ketones: The reaction of chlorine with organics in water may yield various chlorinated acids, alcohols, aldehydes, and ketones in addition to the THMs. EPA is evaluating whether MCLGs should be developed for:

Monochloroacetic acid	1,1-Dichloroacetone
Dichloroacetic acid	1,3-Dichloroacetone
Chloroacetaldehyde	Dichloroacetaldehyde
Chloralhydrate	

Currently available toxicity information on the health effects of these substances is limited.

Haloacetonitriles, Chloropicrin, and Cyanogen Chloride: Bromochloroacetonitrile (BCAN), dibromoacetonitrile (DBAN), dichloroacetonitrile (DC-AN), and trichloroacetonitrile (TCAN) are also products of the reaction between chlorine and organics in water.

Chlorophenols: Mono-, di-, and trichlorophenol (CP, DCP, and TCP) are potential by-products of chlorination formed when chlorine reacts with phenolic materials. They pose common taste and odor problems in addition to their possible toxic properties.

2.3.5.4 *Other Disinfectants*

Other disinfectants or treatment practices have been used in drinking water disinfection. These include ozone, iodine, bromine, potassium permanganate, silver, ferrate, high pH, ionizing radiation, and UV light. The information available for these substances and treatment practices is extremely limited.

Table 2-12. Contaminants Scheduled for Regulation by 1990 Under the 1986 Amendments to the Safe Drinking Water Act

Methylene chloride (Dichloromethane)	Legionella	Antimony	Adipates	Radium-226
Trichlorobenzene	Standard plate count	Beryllium	Dalapon	Radium-228
		Cyanide	Dinoseb	Radon
		Nickel	Diquat	Uranium
		Sulfate	Endothall	Gross alpha particle radioactivity
		Thallium	Endrin	Beta particle radioactivity
			Glyphosphate	Photon radioactivity
			Hexachlorocyclopentadiene	
			PAHs	
			Phthalates	
			Picloram	
			Simazine	
			2,3,7,8-TCDD (Dioxin)	
			1,1,2-Trichloroethane	
			Vydate (Oxamyl)	

compounds that occur in water. Each reacts individually and can exist in different forms depending on dosages, pH, temperature, amount of organic substances in the water, and oxidation reduction processes that might have occurred.

More generally, disinfectants can be termed oxidants because they oxidize the water and other substances in it, e.g., nitrite. They also assist in floc formation and removal of color from the water. The pH of the water, which may be regulated to control corrosivity, significantly affects the potency of some disinfectants. All of these competing considerations are involved in EPA's current analyses.

Proposed disinfection treatment requirements and by-product regulations are scheduled for proposal in 1990 and promulgation in 1991. Much research remains to be done before the database for these comprehensive regulations is sufficient to formulate MCLs and MCLGs. Table 2-13 shows the drinking water disinfectants and disinfection by-products for which EPA is considering the development of MCLGs and MCLs (19).

Following is a brief summary of health effects and issues of concern for each disinfectant and disinfection by-product category being considered for regulation.

Table 2-13. Disinfectants and Disinfection By-Products Considered for Development of MCLGs and MCLs

Disinfectants
Chlorine
Chlorine dioxide
Chloramine
Disinfection By-Products
Trihalomethanes:
Chloroform
Bromoform
Bromodichloromethane
Dibromochloromethane
Chlorinated acetic acids
Chlorinated alcohols
Chlorinated aldehydes
Chlorinated ketones
Chlorite and chlorate
Chlorophenols
Chloropicrin
Cyanogen chloride
Haloacetonitriles
Ozone by-products
n-Organochloramines
MX (3-chloro-4-dichloromethyl-5-hydroxy-2(5-H)-furanome)

2.3.5.2 *Disinfectants*

Chlorine: Chlorine has been the most widely used disinfectant in the U.S. for more than 60 years (20). Despite its long and widespread use, very little information exists on the low-level health effects of ingested chlorine; most laboratory studies have used inhalation as the route of exposure to this chemical. The acute toxicity of chlorine in amounts found in drinking water appears to be relatively low. Additional chronic data and resolution of the issues concerning chlorine's carcinogenicity or cardiovascular toxicity are needed before an MCLG can be determined.

Chlorine Dioxide, Chlorite, and Chlorate: Chlorine dioxide (ClO_2) has often been used in conjunction with chlorine to control phenolic tastes and odors (21). It was first used in the U.S. during World War II when chlorine was in short supply. Although

All surface water systems must filter unless they meet source water quality criteria and site-specific conditions.

Only qualified operators will be entitled to operate the systems. All systems will need to achieve at least 99.9 percent removal and/or inactivation of Giardia cysts and 99.99 percent removal and/or inactivation of enteric viruses.

Filtration is not required if a system meets:

- Source water quality criteria (coliform and turbidity levels)
- The following site-specific conditions:

  1. Achieves disinfection rate of 99.9 and 99.99 percent inactivation of Giardia and viruses respectively
  2. Maintains watershed control/satisfies on-site inspection requirements
  3. Has no history of waterborne disease outbreaks that were not followed by treatment corrections
  4. Complies with the revised coliform MCL (unless the state determines that the violation was not caused by a treatment deficiency of the source water)
  5. Meets the total trihalomethanes (TTHM) MCL (for systems over 10,000 people)

Finally, local water system operators must report to their state governments monthly on their progress in meeting federal rules and must report within 48 hours any waterborne disease outbreaks. Operators of both filtered and unfiltered water systems must meet federal requirements within 4 years of issuance of the final rule.

2.3.3 MCLs/MCLGs by December 1988: Radionuclides

The existing NIPDWRs include both natural and manmade radionuclides. The standards for natural radionuclides include a gross alpha particle standard of 15 pCi/L and a combined radium-226 and radium-228 standard of 5 pCi/L. Both radon and uranium were excluded from the interim regulations because of lack of data regarding their occurrence and toxicity. The interim standard for manmade radionuclides is a total dose equivalent to 4 millirems (mrems) per year.

The MCLGs under development for radionuclides apply to natural uranium, radon-222, gross alpha particle activity (probably as a monitoring screen), beta and photon emitters (manmade radionuclides), and separate values for radium-226 and radium-228. All these pollutants are estimated to pose carcinogenic risks to humans. The House Report that accompanied the SDWA states that when there is no threshold in the dose-response curve for a drinking water contaminant (i.e., a carcinogen), the MCLGs must be set at zero. This is because the MCLG must be set at a level for which there are no known or anticipated adverse health effects.

2.3.4 MCLs/MCLGs by June 1989: Other Inorganic Chemicals, Synthetic Organic Chemicals, and Pesticides

Contaminants slated to be regulated by June 1989 are shown in Table 2-12. Included are representatives from all five categories of contaminants, including the first NPDWRs for radionuclides. EPA may make up to seven substitutions to this list if the Agency determines that regulation of a different chemical is likely to be more protective of public health.

2.3.5 MCLs/MCLGs by January 1991:Disinfectants and Disinfection By-Products

The EPA is required to specify criteria for the disinfection of public water supplies. As EPA develops regulations for disinfection and disinfection by-products, it must consider the relationship between the benefits of disinfectants and any adverse health effects brought about by their use. More specifically, since the SDWA requires that disinfection be specified as a treatment technique for all public water systems, EPA must determine the conditions under which disinfection must be used and the con-ditions under which disinfectant residues do not adversely affect public health.

2.3.5.1 Background

Public water systems use disinfection to control pathogenic microorganisms and thus reduce the risk of waterborne disease. The introduction of disinfectants into the water supply, however, has resulted in undesirable by-products with toxic properties that have caused other health risks.

Trihalomethanes (THMs), one family of the disinfection by-products, are currently regulated. These compounds are formed in drinking water during the reaction between chlorine, an effective and widely used disinfectant, and organic matter already in the water. In order to reduce formation of THMs during water treatment, alternative disinfectants are being used to replace free chlorine. These alternatives, however, may produce other by-products that can be toxic under some conditions.

Because disinfectants are chemically very reactive substances, they react quickly with the many organic

For inorganics, proposed BAT treatment techniques may be found in Table 2-11.

Table 2-11. Proposed BAT for Inorganic Chemicals

Chemical	BAT
Asbestos	Coagulation/Filtration Corrosion control
Barium	Ion exchange Lime softening Reverse osmosis
Cadmium	Ion exchange Reverse osmosis Coagulation/Filtration Corrosion control Lime softening
Chromium	Coagulation/Filtration Ion exchange Lime softening (chromium III only) Reverse osmosis
Mercury	Granular activated carbon Coagulation/Filtration and powdered activated carbon* Lime softening Reverse osmosis
Nitrate/Nitrite	Ion exchange Reverse osmosis Oxidation (Nitrite)
Selenium	Activated alumina Lime softening Coagulation/Filtration (selenium IV only) Reverse osmosis

*Mercury influent concentrations < 10 µ/L.

The same BAT is specified for variances under inorganics . Monitoring and reporting requirements and compliance determination, analytical methods of detection, lab certification criteria, monitoring for unregulated contaminants, and regulatory impact analysis are also stipulated.

2.3.2.2 *Microbials and Surface Water Treatment*

Drinking water treatment in the U.S. is among the best in the world. While treatment may be adequate at the drinking water source, however, the condition of the distribution system may permit regrowth of microbial, bacterial, and viral contaminants. These two treatment rules will standardize and upgrade monitoring and treatment processes and disinfection standards, thus eliminating thousands of cases of waterborne disease. EPA's current standards, in effect since 1977, protect for coliform bacteria and turbidity.

In recent years, Legionnaire's disease and giardiasis (also called backpacker's disease) have made the public increasingly aware of waterborne disease outbreaks. Local water suppliers throughout the U.S. will now be directed by EPA to filter their water and/or disinfect it under certain specified conditions to protect against coliform bacteria, Giardia, heterotrophic bacteria, Legionella, turbidity, and viruses. These contaminants are described below.

Coliform bacteria come from human and animal waste. While common in the environment and generally not harmful themselves , bacteria indicate that the water may be contaminated with disease-causing organisms. Total coliform bacteria regulations apply to all 200,000 public ground-water and surface-water systems (both community and noncommunity supplies). The final rule of June 29, 1989 (effective December 31, 1990) bases compliance on the presence or absence of total coliform in a sample rather than on an estimate of coliform density, as per the current regulations. For more information on monitoring requirements for different systems, see the published final rule in the *Federal Register* (17).

Giardia are protozoa that originate in human and animal waste. Giardiasis, the disease they cause, has flu-like symptoms that can be severe, causing diarrhea, nausea, and dehydration that can last for months. Backpackers who drink from unfiltered, nondisinfected mountain streams often contract giardiasis. Because of their size, Giardia can be filtered out of water or alternatively can be inactivated by a rigorous disinfection process.

Heterotrophic bacteria are organisms that use only organic materials as their food source. Turbidity is a measure of the cloudiness of water, which is indicative of excess organic material (including animal or human waste). Therefore, testing for heterotrophic bacteria and turbidity can point to the presence of disease-causing microorganisms and can provide information on the effectiveness of treatment processes.

Legionella are bacteria that cause severe pneumonia-like symptoms (i.e., Legionnaire's disease), especially in a weaker population such as the elderly. Viruses cause such diseases as hepatitis-A and gastro-enteritis.

Many water supply systems do not filter or disinfect their water. Of the 9,800 drinking water systems in the U.S. using surface water, 3,000 systems serving approximately 21 million people currently do not filter. The final rule of June 29, 1989 (effective December 31, 1990) sets criteria for the states to determine which water systems will have to install filtration or update existing filtration facilities and/or disinfect (18):

- All surface water systems will now have to disinfect.

Table 2-10. Proposed MCLs/MCLGs for Second Phase of Regulatory Efforts

Chemical	Proposed MCL (mg/L)	Proposed MCLG (mg/L)
	Inorganic Chemicals	
1. Asbestos	7 million fibers/L*	7 million fibers/L*
2. Barium	5	5
3. Cadmium	0.005	0.005
4. Chromium	0.1	0.1
5. Mercury	0.002	0.002
6. Nitrate	10 (as N)**	10 (as N)**
7. Nitrite	1 (as N)	1 (as N)
8. Selenium	0.05	0.05
	Synthetic Organic Chemicals	
1. Acrylamide	Treatment technique	zero
2. Alachlor	0.002	zero
3. Aldicarb	0.01	0.01
4. Aldicarb sulfoxide	0.01	0.01
5. Aldicarb sulfone	0.04	0.04
6. Atrazine	0.003	0.003
7. Carbofuran	0.04	0.04
8. Chlordane	0.002	zero
9. Dibromochloropropane	0.0002	zero
10. o-Dichlorobenzene	0.6	0.6
11. cis-1,2-Dichloroethylene	0.07	0.07
12. trans-1,2-Dichloroethylene	0.1	0.1
13. 1,2-Dichloropropane	0.005	zero
14. 2,4-D	0.07	0.07
15. Epichlorohydrin	Treatment technique	zero
16. Ethyl benzene	0.7	0.7
17. Ethylene dibromide	0.00005	zero
18. Heptachlor	0.0004	zero
19. Heptachlor epoxide	0.0002	zero
20. Lindane	0.0002	0.0002
21. Methoxychlor	0.4	0.4
22. Monochlorobenzene	0.1	0.1
23. PCBs	0.0005	zero
24. Pentachlorophenol	0.2/0.0001†	0.2/0
25. Styrene	0.005/0.1***	zero/0.1***
26. Tetrachloroethylene	0.005	zero
27. Toluene	2.0	2.0
28. Toxaphene	0.005	zero
29. 2,4,5-TP	0.05	0.05
30. Xylenes (total)	10.0	10.0

* Fibers longer than 10 μm.
** MCL and MCLG for total nitrate and nitrite = 10 mg/L (as N).
*** MCL of 0.1 mg/L and MCLG of 0.1 mg/L based on Group C classification and MCL of 0.005 mg/L and MCLG of zero based on Group B2 classification.
† Issue on cancer classification and quantitation.

Table 2-9. Unregulated Contaminants Under SDWA Section 1445

List 1: Monitoring Required for All Systems

Bromobenzene	1,1-Dichloroethane
Bromodichloromethane	1,1-Dichloropropene
Bromoform	1,2-Dichloropropane
Bromomethane	1,3-Dichloropropane
Chlorobenzene	1,3-Dichloropropene
Chlorodibromomethane	2,2-Dichloropropane
Chloroethane	Ethyl benzene
Chloroform	Styrene
Chloromethane	1,1,2-Trichloroethane
o-Chlorotoluene	1,1,1,2-Tetrachloroethane
p-Chlorotoluene	1,1,2,2-Tetrachloroethane
Dibromomethane	Tetrachloroethylene
m-Dichlorobenzene	1,2,3-Trichloropropane
o-Dichlorobenzene	Toluene
trans-1,2-Dichloroethylene	*p*-Xylene
cis-1,2-Dichloroethylene	*o*-Xylene
Dichloromethane	*m*-Xylene

List 2: Monitoring Required for Vulnerable Systems

Ethylene dibromide (EDB)	1,2-Dibromo-3-chloropropane (DBCP)

List 3: Monitoring Required at the State's Discretion

Bromochloromethane	*n*-Propylbenzene
n-Butylbenzene	*sec*-Butylbenzene
Dichlorodifluoromethane	*tert*-Butylbenzene
Fluorotrichloromethane	1,2,3-Trichlorobenzene
Hexachlorobutadiene	1,2,4-Trichlorobenzene
Isopropylbenzene	1,2,4-Trimethylbenzene
p-Isopropyltoluene	1,3,5-Trimethylbenzene naphthalene

geological formations. Some are also consistently found in drinking water supplies from manmade sources; i.e., copper, lead, chromium, and asbestos pipes and plumbing supplies. These metals either leach into water sources naturally or as a result of corrosion of the pipes and plumbing.

Lead, an inorganic metal of great concern when found in drinking water, was originally handled under the second phase of the regulations, but it has now been addressed in a separate rule along with copper. Lead contamination in water entering the public distribution system is rare. Instead, lead contamination is caused mostly by corrosion of lead piping, solder, and flux in public water systems and plumbing.

The proposed rule of August 18, 1988 (for both lead and copper) specified an MCL for lead of 0.005 mg/L for water leaving the treatment plant (current NIPDWR = 0.050 mg/L) and an MCLG of zero. In addition, another lead standard of 0.01 mg/L was proposed for an average of a representative number of samples from consumers' taps (16). In the proposed rule, systems exceeding the at-the-tap limit will be required to implement corrosion control and/or corrosion inhibition. The proposed rule also includes public notice requirements.

As of June 19, 1986, the SDWA amendments prohibited the use of lead piping, solder, and flux in material in contact with potable water. The amendments also required public water systems to identify and provide notice to persons who may be affected by lead contamination of their drinking water.

Secondary MCLs (SMCLs) are aesthetic drinking water standards based on color, odor, and taste. SMCLs are being proposed under Phase II for aluminum and silver.

The best available technology (BAT) for all synthetic organic chemicals except acrylamide and epichlorohydrin is granular activated carbon (GAC). BAT for those two chemicals is polymer addition practices (PAP). Packed tower aeration (PTA), in addition to granular activated carbon, will be specified for dibromochloropropane, 1,2-dichloropropane, *cis*-1,2-dichloroethylene, *trans*-1,2-dichloroethylene, *o*-dichloro-benzene, ethylene dibromide, ethylbenzene, monochlorobenzene, styrene, tetrachloroethylene, toluene, and xylene.

persons (i.e., workplaces, offices, and schools) that have their own water supplies and from which users consume from one-third to one-half or more of their normal daily water consumption.

The rule also specifies the monitoring of contaminants that are not regulated as NPDWRs, as required by Section 1445 of SDWA. Each public water system must monitor at least once every 5 years for unregulated contaminants, unless EPA requires more frequent testing. The monitoring data will assist EPA in determining whether regulations for these contaminants will be necessary, and if so, what levels might be appropriate.

EPA has chosen 51 unregulated chemicals for monitoring (see Table 2-9) and separated them into three groups (13):

- List 1: Chemicals for which monitoring is required for all CWSs and NTNCWSs. Compounds can be readily analyzed.
- List 2: Chemicals for which monitoring is required only for systems vulnerable to contamination by these compounds. Compounds have limited localized occurrence potential and require some specialized handling.
- List 3: Chemicals for which the state decides whether a system must monitor. These are compounds that do not elute within reasonable retention time using packed column treatment methods or are difficult to analyze because of high volatility or instability. They are much less likely to be present in drinking water.

The monitoring methods for the unregulated VOCs are similar to those required for the regulated VOCs. As a result, water systems will be encouraged to use the same samples for all of the analyses, and to have the analyses of the unregulated VOCs performed with the analyses for the regulated VOCs, thereby reducing costs for both sampling and analysis.

This list also outlines some of the disinfection by-products that are scheduled to be promulgated as part of Phase IV of the regulatory program. Other disinfection by-products will be extracted from the Drinking Water Priority List (DWPL).

Along with the VOC rule, two proposals were announced: the list of changes on and off the original list of 83 contaminants and a list of 25 additional substances (14). The lists of both proposals were added to the DWPL, the final version of which was published January 22, 1988.

2.3.2 MCLs/MCLGs by June 1988: Organics, Inorganics, Microbials, and Filtration

The second phase of regulations is designed to respond to the statutory requirements of the SDWA and Amendments to set 40 MCLGs and MCLs (plus the monitoring of 51 contaminants) by June 1988. Also scheduled to be established by June 1988 were microbial contaminants and filtration criteria, a proposed rule for which was published November 3, 1987. The June 1988 statutory deadline has not been met.

The list of chemicals proposed on November 13, 1985 only included MCLGs. Since then the SDWA Amendments have superseded this proposal, stipulating that MCLs and MCLGs must be promulgated simultaneously. Promulgation has been slower for these chemicals because few data are available on their occurrence in drinking water, or on the treatment technologies required. However, there is enough information, as specified by law, to regulate these contaminants.

2.3.2.1 Organics and Inorganics

The second phase covers 30 synthetic organic chemicals and 8 inorganic chemicals (see Table 2-10) (15). These 38 chemicals represent a widely varied group of contaminants, each causing a unique problem. The synthetic organics may be found near manufacturing; pesticides near agricultural development; and the inorganics both in natural geologic formations and in treatment and conveyance mech-anisms for drinking water supplies and sources.

The health effects produced by these chemicals are as varied as their uses. Some are potent neurotoxins, others are organ-specific toxicants, and some are animal or human carcinogens. Thus, the approach to setting MCLs and MCLGs for each chemical must be very comprehensive.

Over half of the organics are pesticides, which have been frequently detected in drinking water. Unlike other synthetic organics used in manufacturing products and as additives, pesticides are manufactured to be toxic. They are applied directly to the ground to kill pests or, in the case of herbicides registered for aquatic applications, are applied directly to water or migrate to drinking water sources from runoff. Their widespread use and direct access to water supplies make them of special concern for drinking water contamination.

In general, inorganic chemicals are naturally occurring contaminants prevalent in natural

Table 2-8. VOCs: Final MCLGs and MCLs (in mg/L)

Contaminant	Health Effect	EPA Class	Final MCLG	Final MCL
Vinyl chloride	Human carcinogen	A	zero	0.002
Benzene	Human carcinogen	A	zero	0.005
Trichloroethylene	Probable carcinogen	B2	zero	0.005
Carbon tetrachloride	Probable carcinogen	B2	zero	0.005
1,2-Dichloroethane	Probable carcinogen	B2	zero	0.005
para-Dichlorobenzene	Possible carcinogen	C	0.075	0.075
1,1-Dichloroethylene	Possible carcinogen	C	0.007	0.007
1,1,1-Trichloroethane	Liver, circulatory system, and central nervous system (CNS) damage	D	0.2	0.2

(PTA) as best available technology (BAT) for removing all VOCs , except vinyl chloride, for which only PTA is designated BAT. These technologies have 90-99 percent removal efficiency, are commercially available, and have been used successfully to remove VOCs in ground water from both influents and ef-fluents in many locations throughout the U.S.

Note that in Table 2-8, for all the chemicals with zero MCLGs except vinyl chloride, the MCLs are set at 0.005 mg/L. This number represents the "feasible" level taking cost into consideration. With an MCL of 0.005 mg/L, only 1,300 community water systems (CWSs) need to install treatment capabilities to satisfy the requirements, incurring a total capital cost of $280 million.

The MCL for vinyl chloride – 0.002 mg/L – does not result in any increased costs for public water systems. Very few, if any, would have to install treatment solely to control vinyl chloride. Systems contaminated with any level of this chemical virtually always contain one or more of the other VOCs, since vinyl chloride is known to be a degradation product of PCE or TCE.

PTA removes vinyl chloride to a 0.002 mg/L level. Although this level may be harder to measure than 0.005 mg/L, EPA recognizes that vinyl chloride is a human carcinogen of possibly higher potency than the other VOCs listed on Table 2-8. Thus, the risk posed by each unit of exposure could be higher than the equivalent unit of any of the other VOCs with a zero MCLG.

In addition to establishing MCLGs and MCLs for the eight VOCs, this rule specifies the following conditions for regulating those chemicals:

BAT for treatment for the purpose of variances to be set when MCLs are set (as per SDWA Sections 1412 and 1415)

Monitoring requirements and compliance determination

Public notification and reporting requirements

Laboratory certification criteria

Allowable point-of-entry (POE) and point-of-use (POU) devices and bottled water uses to achieve compliance

Variances and exemptions of control techniques for VOCs

An additional definition was added for public water systems for which directives of this rule apply. Public water systems are divided into community and noncommunity systems. A community water system (CWS) is one that serves at least 15 connections used by year-round residents or regularly serves at least 25 year-round residents. Noncommunity water systems (NCWSs) are, by definition, all other water systems and include transient systems (i.e., campgrounds, gas stations) and nontransient systems (i.e., schools, workplaces, hospitals) that have their own water supplies and serve the same population over 6 months of a year.

EPA has promulgated a definition of a "nontransient noncommunity water system" (NTNCWS) and applied it to the NPDWRs for the eight VOCs in addition to the already defined systems. A noncommunity nontransient water system is "a public water system that is not a regular community water system and that supplies at least 25 of the same people over 6 months per year" (12).

The purpose of the change was to protect nonresidential populations of more than 25 people who, because of regular long-term water usage, incur risks of adverse health effects similar to those incurred by residential populations. The change was designed to include systems serving more than 25

- The contaminant must have a documented or suspected adverse human health effect.
- There must be sufficient information available on the contaminant so that a regulation could be developed within the statutory time frames. Substances for which insufficient information for regulation is available will be candidates for subsequent priority lists.

Further information on the specific selection criteria may be found in the *Federal Register*, 52 FR 25720 (10).

The seven contaminants substituted onto the original list of 83 contaminants are aldicarb sulfoxide, aldicarb sulfone, heptachlor, heptachlor epoxide, styrene, ethyl benzene, and nitrite.

The contaminants removed from the original list of 83 contaminants, as listed below, will now be placed on the DWPL (see also Table 2-7):

- Zinc, sodium, vanadium, silver, molybdenum, dibromomethane, aluminum

Monitoring requirements are to be set to ensure compliance with the MCLs. In all but three cases, states have the responsibility for enforcement of MCLs. Public water systems must give public notification of a violation of an MCL or monitoring requirement.

Other priorities set by the SDWA, such as compliance requirements, surface water treatment and disinfection criteria, variances and exemptions, and regulatory timetables and deadlines, are discussed briefly in each of the regulatory phase sections below.

2.3 Specific Phases of Regulatory Efforts by the Office of Drinking Water

The Office of Drinking Water has outlined a six-phase plan (see top of next column)

2.3.1 Volatile Organicc Chemicals - Promulgated July 8, 1987

On July 8, 1987, the final rule was published for NPDWRs for eight volatile organic chemicals. Monitoring for unregulated contaminants (11) was also covered. The VOCs listed in this rule, plus fluoride (promulgated April 6, 1986), satisfied the statutory deadlines of SDWA, which required the establishment of the first 9 MCLs within 12 months. MCLs and MCLGs for the eight VOCs are shown in Table 2-8.

Phase	Substances	Expected Promulgation Date
I	Volatile organic chemicals (VOCs)	July 8, 1987
II	Synthetic organic chemicals (SOCs), Inorganic chemicals (IOCs), Microbial and surface water treatment (Filtration)	December 1990
	Lead/Copper (corrosion by-products)	December 1988
III	Radionuclides (proposal)	February 1991
IV	Disinfectants and disinfection by-products	January 1992
V	Other IOCs, SOCs, and pesticides	June 1991
VI	Additional DWPL chemicals	January 1992

These six regulatory phases parallel the SDWA-specified deadlines, listed below:

9 MCLGs and MCLs + monitoring	June 19, 1987
Public notice revisions	September 19, 1987
Filtration criteria	December 19, 1987
Monitoring for unregulated contaminants	December 19, 1987
Final list of contaminants on DWPL	January 1, 1988
40 MCLGs and MCLs + monitoring	June 19, 1988
34 MCLGs and MCLs + monitoring	June 19, 1989
Disinfection treatment	June 19, 1989
25 MCLGs and MCLs + monitoring	January 1, 1991

The eight synthetic VOCs shown in Table 2-8 are widely used in products such as unleaded gas additives; household cleaning solutions; solvents for removing grease from clothes, electronics, and aircraft engines; air freshen-ers; and mothballs. They are found frequently in drinking water from groundwater sources. All have relatively low boiling points and vaporize readily.

EPA proposed the MCLs for these chemicals based on an evaluation of 1) the availability and performance of treatment technologies for the VOCs; 2) the availability, performance, and cost of analytical methods; and 3) the costs of applying the various technologies to reduce VOCs to various concentrations.

In reviewing the different technologies available for VOC removal, EPA considered the following criteria: removal efficiency, degree of compatibility with other treatment processes, service life, and ability to achieve compliance.

Based on these criteria, EPA proposed granular activated carbon (GAC) and packed tower aeration

Table 2-6. Contaminants Required to Be Regulated Under the Safe Drinking Water Act Amendments of 1986

Volatile Organic Chemicals	
Trichloroethylene*	Benzene*
Tetrachloroethylene*	Monochlorobenzene
Carbon tetrachloride*	Dichlorobenzene**
1,1,1-Trichloroethane*	Trichlorobenzene
Dichloroethane*	1,1-Dichloroethylene*
Vinyl chloride*	trans-1,2-Dichloroethylene
Methylene chloride	cis-1,2-Dichloroethylene
Microbiology and Turbidity	
Total coliforms	Viruses
Turbidity	Standard plate count
Giardia lamblia	Legionella
Inorganics	
Arsenic	Molybdenum
Barium	Asbestos
Cadmium	Sulfate
Chromium	Copper
Lead	Vanadium
Mercury	Sodium
Nitrate	Nickel
Selenium	Zinc
Silver	Thallium
Fluoride***	Beryllium
Aluminum	Cyanide
Antimony	
Organics	
Endrin	1,1,2-Trichloroethane
Lindane	Vydate (Oxamyl)
Methoxychlor	Simazine
Toxaphene	Polyaromatic hydrocarbons
2,4-D	Polychlorinated biphenyls
2,4,5-TP	Atrazine
Aldicarb	Phthalates
Chlordane	Acrylamide
Dalapon	Dibromochloropropane
Diquat	1,2-Dichloropropane
Endothall	Pentachlorophenol
Glyphosphate	Pichloram
Carbofuran	Dinoseb
Alachlor	Ethylene dibromide
Epichlorohydrin	Dibromomethane
Toluene	Xylene
Adipates	Hexachlorocyclopentadiene
	2,3,7,8-TCDD (Dioxin)
Radionuclides	
Radium-226 and -228	Gross alpha particle activity
Beta particle and photon radioactivity	Uranium
	Radon

* Promulgated July 8, 1987
** MCL for p-dichlorobenzene has been published;ortho-dichlorobenzene is on additional list for consideration.
*** Promulgated April 2, 1986

MCLs and MCLGs are to be proposed and promulgated simultaneously, thus shortening the standards-setting procedure.

The EPA under the SDWA must maintain a Drinking Water Priority List (DWPL) of contaminants for future regulation (see Table 2-7). The proposed list was published July 8, 1987; the final list was published January 22, 1988 (9). MCLs and MCLGs must be set for at least 25 contaminants on the DWPL by January 1, 1991; every three years thereafter, 25 more MCLs and MCLGs must be set.

Table 2-7. Drinking Water Priority List (53 FR 1901, Jan. 22, 1988)

1,1,1,2-Tetrachloroethane	Cyanazine
1,1,2,2-Tetrachloroethane	Cyanogen chloride
1,1-Dichloroethane	Dibromoacetonitrile
1,1-Dichloropropene	Dibromochloromethane
1,2,3-Trichloropropene	Dibromomethane
1,3-Dichloropropane	Dicamba
1,3-Dichloropropene	Dichloroacetonitrile
2,2-Dichloropropane	ETU
2,4,5-T	Hypochlorite ion
2,4-Dinitrotoluene	Isophorone
Aluminum	Methyl tert-butyl ether
Ammonia	Metolachlor
Boron	Metribuzin
Bromobenzene	Molybdenum
Bromochloroacetonitrile	Ozone by-products
Bromodichloromethane	Silver
Bromoform	Sodium
Bromomethane	Strontium
Chloramines	Trichloroacetonitrile
Chlorate	Trifluralin
Chlorine	Vanadium
Chlorine dioxide	Zinc
Chlorite	o-Chlorotoluene
Chloroethane	p-Chlorotoluene
Chloroform	Halogenated acids
Chloromethane	alcohols, aldehydes,
Chloropicrin	ketones, and other
Cryptosporidium	nitriles

The chemicals listed in Table 2-6 include the seven contaminants taken off the original list of 83; disinfectants and disinfection by-products; the first 50 contaminants specified under Sect-ion 110 of the Superfund Amendments and Re-authorization Act of 1986 (SARA); pesticides included as design-analytes in the National Pesticide Survey (NPS, see Section 2.5.6.2); volatile organic chemicals (VOCs) reported in Section 1445 of SDWA as unregulated contaminants to be monitored; and certain other substances reported frequent-ly and/or occurring at high concentrations in other recent surveys. Criteria for place-ment on the Drinking Water Contaminant Priority List are outlined below:

- The contaminant must occur in public water systems, or its characteristics or use patterns must be such that it has a strong potential to occur in public water systems at levels of concern.

- Technical and economic availability of analytical methods that would be acceptable for accurate determinations of compliance (i.e., practical quantitation levels-see below), limits of analytical detection, laboratory capabilities, and costs of analytical techniques

- Concentrations attainable by application of best technology generally available; levels of chemical concentrations in drinking water supplies; feasibility/reliability of removing contaminants to specific concentrations

- Other factors relating to the "best" means of treatment such as air pollution and waste disposal from the treatment method itself, and possible effects on other drinking water quality parameters

- Costs of treatment to achieve contaminant removal (8).

One of the factors used in setting the laboratory performance requirements for an MCL is the minimum detection limit (MDL). The MDL is the minimum concentration of a substance that can be measured and reported with 99 percent confidence that the true value is greater than zero. These MDLs are measured by a few of the most experienced labs under nonroutine and controlled conditions.

A second measurement used by EPA, the practical quantitation level (PQL), is not lab- or time-specific and can provide a uniform concentration measurement for setting standards. The PQL is the lowest measurement level that can be reliably achieved within specified limits of precision and accuracy during routine laboratory operating conditions. PQLs are based on four factors: 1) quantitation, 2) precision and accuracy, 3) expected normal laboratory operations, and 4) the fundamental need of the compliance and monitoring program to have a sufficient number of labs available to conduct analyses.

Evaluating treatment technologies is part of regulating chemicals or groups of chemicals. Both available treatment technologies and analytical methods are key to analyzing the regulatory and economic consequences considered for each contaminant. How to monitor, measure, and treat for a specific contaminant (or mixture of contaminants) is published as an integral part of any standard that is promulgated. Regulations for some chemicals must specify the best available technology (BAT) for treatment procedures.

2.2 Summary of the Regulations Specified Under the 1986 Amendments to the Safe Drinking Water Act

The Safe Drinking Water Act was amended in 1986 to require EPA to regulate 83 drinking water contaminants by 1989. An overview of these amendments and the Office of Drinking Water's regulatory program follows.

Recommended Maximum Contaminant Level (RMCL), now termed Maximum Contaminant Level Goal (MCLG).

EPA is to set MCLGs, nonenforceable health goals, and NPDWRs, which consist of MCLs and treatment techniques, for 83 specific contaminants and for any other contaminant in drink-ing water that may have an adverse effect on human health and that is known or anticipated to occur in public water systems (see Table 2-6).

The Act requires EPA to regulate drinking water contaminants according to the following schedule :

- 9 MCLs in 12 months: June 19, 1987
- 40 MCLs in 24 months: June 19, 1988
- 34 MCLs in 36 months: June 19, 1989

EPA is allowed to substitute up to seven contaminants for ones on the above list if they are found to be more harmful to public health.

MCLs are to be set as close to MCLGs as is feasible. The term "generally available" technology was changed to "as is feasible." As discussed earlier, feasible is defined as "with the use of the best technology, treatment techni-ques, or other means which the Administrator finds are available (taking cost into consider-ation) after examination for efficacy under field conditions and not solely under laboratory conditions."

EPA is required to prepare a Report to Congress comparing the benefits and risks of treatment versus no treatment (final report submitted in November 1988).

Granular activated carbon (GAC) is stated in the SDWA as feasible for the control of synthetic organic chemicals (SOCs), and any techno-logy or other means found to be "best available" for control of SOCs must be at least as effective in controlling SOCs as GAC.

Table 3-4. Summary of Toxicity Tests (4)

Acute (Oral LD_{50})	Acute Dermal	Acute Inhalation (LC_{50})	Primary Skin Irritation	Primary Eye Irritation	Skin Sensitization (Allergies)	Subacute	Subchronic	Chronic
• Gavage • Mouse and rat most often used (sometimes also rabbit and dog) • Often starve animals for 16 hours before exposure • Usually administer constant concentration for various doses rather than constant volume • Typical observations: - Observe animals at 1,2, 4 hours and daily for 14 days - Record body weight at 14 days - Minimal or no histo-pathology or clinical chemistry (except in the dog)	• Albino rabbits used • Area of application is free of hair and abraded • If sub-stance is solid, is moistened with saline • Kept in contact with skin for 24 hours • Observe for 2 weeks	• Similar to acute oral LD_{50} • Typical 4-hour exposure	• Rabbits (Draize test) used • Hair clipped • 0.5 mL liquid or 0.5 g solid • Covered by gauze and then plastic • Kept in contact with skin for 4 hours • Swelling and redness scored at 24 and 72 hours after appli-cation	• Rabbits used • Place liquid or unmoisten-ed solid in one eye (0.1 mL liquid or 100 mg solid) • Other eye serves as control • Eye irritation graded and scored at 1, 2, 3, 4, and 7 days and every 3 days thereafter until toxicity subsides	• Guinea pigs used • Tests used include: - Draize - Buehler occluded patch - Magnus-son and Kligman maximi-zation	• To determine dose levels for subchronic study • Typical protocol: - 14-day duration - In rodents, 4 doses;10 animals per sex per dose; in dogs, 3 doses, 3 dogs per sex per dose - Observe twice a day - Perform clinical chemistry, histopatho-logy, etc.	• Typical protocol: - 90 days (13 weeks) dura-tion - At least 3 doses and controls - 2 species (15 rats of each sex per dose and 4 dogs of each sex per dose) - Route of intended use or exposure (usually diet) • Typical observations: - Mortality - Body weight changes - Urinalysis - Hematology - Clinical chemistry - Gross and microscopic examination of several parts of the body	• Similar to subchronic but longer duration • Duration depends on intended period of exposure in man. Can be as little as 6 months or as long as lifetime of animal (i.e., 2 years in rats). Start with 60 rats per sex per dose to ensure that 30 survive. • For dogs, often use 3 doses and 6 males and 6 females per dose. Typical duration is 12 months; clinical chemistry performed before exposure and at 1, 3, 6, 9, and 12 months. • Typical observations: - See subchronic - In dogs, often perform ophthalmic examination every 6 months

(continued)

MTD and one-half of the MTD are the usual doses used in a NCI carcinogenicity bioassay.

The main reason cited for using the MTD as the highest dose in a bioassay is that experimental studies are conducted on a small scale, making them statistically insensitive, and that very high doses overcome this problem. Due to cost considerations, experiments are carried out with relatively small groups of animals. Typically, 50 or 60 animals of each species and sex will be used at each dose level, including the control group. At the end of such an experiment, the examining pathologists tabulate the incidence of cancer as a function of dose (including control animal incidence). Statisticians then analyze the data to determine whether any observed differences in tumor incidence (fraction of animals hav-ing a tumor of a certain type) are due to random variations in tumor incidence or to exposure to the substance.

Selection of Animal Species: Rats and mice are the most commonly used laboratory animals for toxicity testing. They are inexpensive and can be handled relatively easily, and, such factors as genetic background and disease susceptibility are well established for these species. The full life spans of these smaller rodents are complete in 2 to 3 years, so the effects of lifetime exposure to a substance can be measured relatively quickly.

Other rodents such as hamsters and guinea pigs are also used, as well as rabbits, dogs, and primates such as monkeys or baboons. Reproductive studies often use primates because their reproductive systems are similar to that of humans. Rabbits are often used for testing dermal toxicity because their shaved skin is more sensitive than that of other animals.

Dose and Duration: Determining the LD_{50} is frequently the first toxicity experiment performed. After completing this effort, investigators study the effects of lower doses administered over longer periods to find the range of doses over which adverse effects occur and to identify the NOAEL for these effects (although the NOAEL is not always sought or achieved). A toxicity experiment is of limited value unless a dose of sufficient magnitude to cause some type of adverse effect within the duration of the experiment is achieved. If no effects are seen at any dose administered, the toxic properties of the substance cannot be characterized and the experiment will usually be repeated at higher doses or over a longer timespan.

Some substances with extremely low toxicity must be administered at extremely high levels to produce effects; in many cases, such high levels will cause dietary maladjustments leading to an adverse nutritional effect that confounds interpretation. The highest level of a compound fed to an animal in toxicity studies is 5 percent of the diet, even if no toxic effect is seen at this level.

Studies are frequently characterized according to the duration of exposure. Acute toxicity studies involve a single dose, or exposures of very short duration (i.e., 8 hours of inhalation). Chronic studies involve exposures for nearly the full lifetime of the experimental animals. Experiments of varying duration between these extremes are referred to as subchronic studies.

Number of Dose Levels: Although many different dose levels are needed to develop a well-characterized dose-response relationship, practical considerations usually limit the number to two or three, especially in chronic studies. Experiments involving a single dose are frequently reported, and these leave great uncertainty about the full range of doses over which effects are expected.

Controls: All toxicity experiments require control animals that are not exposed to the substances in question. Control animals must be of the same species, strain, sex, age, and state of health as the treated animals, and must be held under identical conditions throughout the experiment. Indeed, allocation of animals to control and treatment groups should be performed on a completely random basis. Other controls are historical; i.e., data on what has happened in the past with that species and strain of experimental animal.

Route of Exposure: Animals are usually exposed by a route that is as close as possible to the route by which humans will be exposed. In some cases, however, the investigator may have to use other routes or conditions of dosing to achieve the desired experimental dose. For example, some substances are administered by stomach tube (gavage) because they are too volatile or unpalatable to be placed in the animals' diets at the high levels needed for toxicity studies.

Summary of Toxicity Studies: Table 3-4 summarizes the major types of toxicity tests currently used. It lists key characteristics of acute tests, chronic tests, and various reproductive system tests. Table 3-5 shows typical costs of some of these tests, which can be quite high. Also noteworthy is the completeness of the various tests often performed on laboratory animals after their exposure to a chemical. These urinalysis, hematology, clinical chemistry, and histopathological tests examine many more parameters than even thorough human autopsies (see Table 3-6).

3.2.1.4 Designing Tests for Carcinogenicity

One of the most complex and important of the specialized tests is the carcinogenesis bioassay. This type of experiment is used to test the hypothesis of carcinogenicity—that is, the capacity of a substance to produce tumors.

In a National Cancer Institute (NCI) carcinogenicity bioassay, the test substance is administered over most of the adult life of the animal, and the animal is observed for formation of tumors. The general principles of test design previously discussed apply to this testing, but one critical and controversial design issue requires extensive discussion: how to use the maximum tolerated dose (MTD). The MTD is the maximum dose that an animal can tolerate for a major portion of its lifetime without significant impairment of growth or observable toxic effect other than carcinogenicity.

Because cancer can take most of a lifetime to develop, scientists widely agree that studies should be designed so that the animals survive in relatively good health for a normal lifetime. Whether the MTD, as currently used, is the best way to achieve this objective, however, is currently under debate. The

increase of tumor incidence in treated versus control animals; dose-related shortening of the time-to-tumor occurrence or time-to-death with tumor; and a dose-related increase in the proportion of tumors that are malignant. The following sections describe animal toxicity studies, including major areas of importance in their design, conduct, and interpretation. Particular consideration will be given to the uncertainties associated with evaluating their results.

3.2.1.2 Interpreting Manifestations of Toxicity

Toxic effects, regardless of the organ or system in which they occur, can take various forms. First, the severity of injury can increase as the dose increases, as happens with some chemicals affecting the liver: High doses kill liver cells, perhaps so many that the liver is destroyed and some or all of the experimental subjects die. As the dose is lowered, fewer cells are killed, but they exhibit other forms of damage that cause imperfections in their functioning. At lower doses still, no cell deaths may occur and only slight alterations in cell function or structure may be noted. Finally, a dose may be achieved at which no effect is observed, or at which there are only biochemical alterations that have no known adverse effects on the health of the animal. (Although some toxicologists consider any such alteration, even if its long-term consequences are unknown, to be "adverse," no clear consensus has been reached on this issue.) One of the goals of toxicity studies is to determine the No-Observed-Adverse-Effect level (NOAEL), which is the dose at which no adverse effect is seen; the role of the NOAEL in risk assessment is discussed further in subsequent sections.

Second, the incidence but not the severity of an effect may increase with increasing dose. In such cases, as the dose increases, the fraction of experimental animals experiencing adverse effects (i.e., the incidence of disease or injury) increases. At sufficiently high doses, all experimental subjects will experience the effect. Thus, increasing the dose increases the probability (i.e., risk) that the abnormality will develop in an exposed population.

Third, both the severity and the incidence of a toxic effect may increase as the level of exposure increases. The increase in severity is a result of increased damage at higher doses, while the increase in incidence is a result of differences in individual sensitivity. In addition, the site at which a substance acts (e.g., liver, kidney) may change as the dose changes. Many toxic effects, including cancer, fall in this category

Generally, as the duration of exposure increases, the two critical doses (the NOAEL and the LOAEL) decrease; in some cases, new effects not seen with exposures of short duration appear after longer exposures.

Toxic effects also vary in degree of reversibility. In some cases, an adverse health effect will disappear almost immediately following cessation of exposure. At the other extreme, some exposures will result in a permanent injury—for example, a severe birth defect from fetal exposure to a substance that irreversibly damaged the fetus at a critical moment of its development. Further, some tissues such as the liver can repair themselves relatively quickly, while others such as nerves have no ability to repair themselves. Most toxic responses fall somewhere between these extremes. In many experiments, however, the degree of reversibility is difficult to ascertain.

The seriousness of a toxic effect must also be considered. Certain types of toxic damage are clearly adverse and are a definite threat to health. However, other types of effects observed during toxicity studies are not clearly of health significance. For example, at a given dose a chemical may produce a slight increase in red blood cell count. If no other effects are observed at this dose, researchers cannot be sure that a true adverse response has occurred. Determining whether such slight changes are significant to health is one of the critical issues in assessing safety.

There are several other important factors to consider when examining toxic effects. A toxic effect can be immediate, such as in poisoning, or delayed, as in cancer. Indeed, cancer typically affects an individual many years after continuous or intermittent exposure to a carcinogen. An effect can be local (i.e., at the site of application) or systemic (i.e., carried by the blood or lymph to different parts of the body). Since the concentrations of substances found in drinking water are usually too low to cause local effects, systemic effects should be considered the key concern in drinking water. Effects can also be "idiosyncratic" - affecting people with a certain genetic predisposition much more than others. Finally, some substances - for example, the oil in poison ivy - cause allergic or sensitization reactions in which production of anti-bodies causes symptoms such as inflammation.

3.2.1.3 Designing and Conducting Toxicity Tests

Toxicity experiments vary widely in design and protocols used. There are relatively well standardized tests for various types of toxicity (i.e., National Cancer Institute carcinogenicity bioassays) developed by regulatory and public agencies in connection with the premarket testing requirements for certain classes of chemicals. However, many other tests and research-oriented investigations are conducted using specialized study designs (i.e., carcinogenicity assays in fish). This section describes a few of the critical considerations associated with designing toxicity experiments.

benzene caused excess production of white blood cells came from a series of case reports), seldom provide the central body of information for risk assessment. For this reason, and because they usually present no unusual problems of interpretation, they are not further reviewed here. Rather, our attention is devoted to the two principal sources of toxicity data: animal tests and epidemiological studies. These two types of investigation can present interpretative difficulties, some subtle, some highly controversial.

3.2.1 Animal Studies

Toxicity studies are conducted to identify the nature of health damage produced by a substance [3] and the range of doses over which damage is produced. The usual starting point for such investigations is a study of the acute (single-dose) toxicity of a chemical in experimental animals. Acute toxicity studies are used to calculate doses that will not be lethal to animals used in toxicity studies of longer durations. Moreover, such studies provide an estimate of the compound's comparative toxicity and may indicate the target organ system for chronic toxicity (e.g., kidney, lung, or heart). Toxicologists examine the lethal properties of a substance and estimate its LD_{50} (lethal dose for 50 percent of an exposed population). A group of well-known substances and their LD_{50} values are listed in Table 3-3.

LD_{50} studies reveal one of the basic principles of toxicology: Not all individuals exposed to the same dose of a substance will respond in the same way. Thus, at a dose of a substance that leads to the death of some experimental animals, other animals will get sick but recover, and still others will not appear to be affected at all. Each of the many different types of toxicological studies has a different purpose. Animals may be exposed repeatedly or continuously for several weeks or months in subchronic toxicity studies, or for close to their full lifetimes in chronic toxicity studies.

3.2.1.1 Using Animal Toxicity Data

Animal toxicity studies are based primarily on the longstanding assumption that effects in humans can be inferred from effects in animals. This principle of extrapolating animal data to humans has been widely accepted in the scientific and regulatory communities. All of the chemicals that have been demonstrated to be carcinogenic in humans (with the possible exception of arsenic) are carcinogenic in some, although not all, experimental animal species.

[3] The term *substance* refers to a pure chemical, to a chemical containing impurities, or to a mixture of chemicals. It is clearly important to know the identity and composition of a test substance before drawing inferences about the toxicity of other samples of the same substance that might have a somewhat different composition.

Table 3-3. Approximate Oral LD_{50} in a Species of Rat for a Group of Well-Known Chemicals (3)

Chemical	LD_{50} mg/kg (ppm)
Sucrose (table sugar)	29,700
Ethyl alcohol	14,000
Sodium chloride (common salt)	3,000
Vitamin A	2,000
Vanillin	1,580
Aspirin	1,000
Chloroform	800
Copper sulfate	300
Caffeine	192
Phenobarbital, sodium salt	162
DDT	113
Sodium nitrite	85
Nicotine	53
Aflatoxin B1	7
Sodium cyanide	6.4
Strychnine	2.5

In addition, the acutely toxic doses of many chemicals are similar in humans and a variety of experimental animals. The foundation of this inference of effects between man and animals has been attributed to the evolutionary relationships between animal species. Thus, at least among mammals, the basic anatomical, physiological, and biochemical parameters are similar across species.

Although the general principle of making such interspecies inferences is well founded, exceptions have been noted. For example, guinea pigs are much more sensitive to dioxin (2,3,7,8-TCDD) than other laboratory animals. Many of these exceptions result from differences in the ways various species handle exposure to a chemical and to differences in metabolism, distribution, and pharmacokinetics of the chemical. Because of these potential differences, it is essential to evaluate all interspecies differences carefully when inferring human toxicity from animal toxicologic studies.

In the particular case of long-term animal studies conducted to assess the carcinogenic potential of a compound, certain general observations increase the overall strength of the evidence that the compound is carcinogenic—for example, an increase in the number of tissue sites affected by the agent or an increase in the number of animal species, strains, and sexes showing a carcinogenic response. Several other factors affect the strength of the evidence, including the occurrence of clear-cut dose-response relationships in the data evaluated; the achievement of a high level of statistical significance of the

Table 3-2. Data and Assumptions Necessary to Estimate Human Dose of a Water Contaminant from Knowledge of Its Concentration (1)

Total Dose Is Equal to the Sum of Doses from Five Routes

Direct Ingestion Through Drinking:

- Amount of water consumed each day (generally assumed to be 2 L for adults and 1 L for 10-kg child)
- Fraction of contaminant absorbed through wall of gastrointestinal tract
- Average human body weight

Inhalation of Contaminants:

- Air concentrations resulting from showering, bathing, and other uses of water
- Variation in air concentration over time
- Amount of contaminated air breathed during those activities that may lead to volatilization
- Fraction of inhaled contaminant absorbed through lungs
- Average human body weight

Dermal Exposure:

- Period of time spent washing and bathing
- Fraction of contaminant absorbed through the skin during washing and bathing
- Average human body weight

Ingestion of Contaminated Food:

- Concentrations of contaminant in edible portions of various plants and animals exposed to contaminated ground water
- Amount of contaminated food ingested each day
- Fraction of contaminant absorbed through wall of gastrointestinal tract
- Average human body weight

Skin Exposure for Contaminated Soil:

- Concentrations of contaminant in soil exposed to contaminated ground water
- Amount of daily skin contact with soil
- Amount of soil ingested per day (by children)
- Absorption rates
- Average human body weight

In general, toxicity studies in experimental animals are of greatest value when experimental exposures mimic the mode of human exposure. If both animals and humans are exposed to a contaminant via drinking water, it is generally assumed that the data in animals can be applied directly to man. When experimental routes differ from human routes (e.g., animal dose via injection; human exposure via drinking water), a correction factor often must be used to apply such data to human exposures.

3.2 Hazard Identification

In identifying hazards, two kinds of data are gathered and evaluated: 1) data on the types of health injury or disease that may be produced by a chemical, and 2) data on the conditions of exposure under which injury or disease is produced. The behavior of a chemical within the body and the interactions it undergoes with organs, cells, or even parts of cells may also be characterized. Such data may be of value in answering the ultimate question of whether the forms of toxicity known to be produced by a substance in one population group or in experimental settings are also likely to be produced in humans. Hazard identification is not risk assessment; this step simply determines whether toxic effects observed in one setting are likely to occur in other settings. In other words: Are substances found to be carcinogenic or teratogenic in experimental animals likely to have the same result in humans?

Researchers obtain information on the toxic properties of chemical substances through animal studies, controlled epidemiological investigations of exposed human populations, and clinical studies or case reports of exposed humans. Other information bearing on toxicity derives from experimental studies in systems other than whole animals (i.e., in isolated organs, cells, subcellular components) and from analysis of the molecular structures of the substances of interest. These last two sources of information are generally considered less certain indicators of toxic potential, and accordingly they receive limited treatment here.

Similarly, clinical studies or case reports, while sometimes very important (the earliest signs that

adults are assumed to consume 2 L of water each day through all uses. Thus, if a substance is present at 10 mg/L (ppm) in water, the average daily individual intake of the substance is:

$$10 \text{ mg/L} \times 2 \text{ L/day} = 20 \text{ mg/day}$$

Toxicity comparisons among different species must take into account size differences, usually by dividing daily intake by the weight of the individual. Thus, for a man of average weight (usually assumed to be 70 kg or 154 lb), the daily dose of this substance is:

$$20 \text{ mg/day} \div 70 \text{ kg} = 0.29 \text{ mg/kg/day}$$

For a person of lower weight, such as a female or child, the daily dose at the same intake rate would be larger. For example, a 50-kg woman ingesting this substance would receive a dose of:

$$20 \text{ mg/day} \div 50 \text{ kg} = 0.40 \text{ mg/kg/day}$$

Using the same equation, a child of 10 kg would receive a dose of 2.0 mg/kg/day. However, children drink less water each day than adults (say, 1 L), so a child's dose would be:

$$10 \text{ mg/L} \times 1 \text{ L/day} \div 10 \text{ kg} = 1.0 \text{ mg/kg/day}$$

In general, the smaller the body size, the greater the dose (in mg/kg/day) received from drinking water. This is also true of experimental animals. Usually rats or mice will receive a much higher dose of drinking water contaminants than humans because of their much smaller body size.

These sample calculations point out the difference in measuring environmental concentrations and dose, at least for drinking water. For air and other media, the relationship between measured environmental concentrations and dose is more complex. Table 3-2 lists the data necessary to obtain dose from data on the concentration of a substance in water through five routes or media.

Each medium of exposure must be treated separately and some calculations are more complex than in the above examples of dose per liter of water. A human may be simultaneously exposed to the same substance through several media (e.g., through inhalation, ingestion, dermal contact). The "total dose" received by an individual is the sum of doses received through each individual route (see Table 3-2).

In some cases, it may not be appropriate to add doses in this fashion since the toxic effects of a substance may depend on the route of exposure. For example, inhaled chromium is carcinogenic to the lung, but it appears that ingested chromium is not. In most cases, however, as long as a substance acts at an internal body site (i.e., acts systemically rather than only at the point of initial contact), it is usually considered appropriate to add doses received from several routes.

Many risk assessors use the terms *exposure* and *dose* synonymously. In this chapter, however, dose means the amount received by the subject and encompasses several factors, including contact with a substance, the size of the dose, the duration of exposure, and the nature and size of the exposed population.

Two additional factors concerning dose and exposure require special attention. The first is the concept of absorption (or **absorbed dose**). The second is the technique of **extrapolation**, or drawing inferences from toxicities observed under one route of exposure to predict the likelihood of toxicity under other routes.

When a substance is ingested in the diet or in drinking water, it enters the gastrointestinal tract. When it is present in air (as a gas, aerosol, particle, dust, fume, etc.), it enters the upper airways and lungs. A substance may also come into contact with the skin and other body surfaces as a liquid or solid. Some substances may cause toxic injury at the point of initial contact (skin, gastrointestinal tract, upper airways, lungs, eyes). Indeed, at high concentrations, most substances will cause at least irritation at these points of contact. However, for many substances, toxicity occurs after they pass through certain barriers (i.e., the wall of the gastrointestinal tract or the skin itself), enter blood or lymph, and gain access to the various organs or systems of the body. Chemicals may be distributed in the body in various ways and then excreted. (However, some chemical types - usually substances with high solubility in fat such as DDT - can be stored for long periods of time, usually in fat.)

Substances vary widely in extent of absorption. The fraction of a dose that passes through the wall of the gastrointestinal tract may be very small (1 to 10 percent for some metals) to substantial (close to 100 percent for certain types of organic molecules). Absorption rates also depend on the medium in which a chemical is present: a substance present in water might be absorbed differently from the same substance present in a fatty diet. These rates also vary among animal species and among individuals within a species.

Ideally, an estimation of a systemic dose should consider absorption rates. Unfortunately, data on absorption are limited for most substances, especially in humans. As a result, absorption is not always included in dose estimation (i.e., by default, it is frequently considered to be complete). Sometimes crude adjustments are made to dose estimations, based on the molecular characteristics of a substance and general principles for the estimation of absorption rates.

Table 3-1. Annual Risk of Death from Selected Common Human Activities (2)

Activity	Number of Deaths in Representative Year	Individual Risk in Representative Year	Lifetime Risk
Coal mining:			
Accident	180	1.30×10^{-3} or 1/770	1/17
Black lung	1,135	8×10^{-3} or 1/125	1/3
Motor vehicle	46,000	3.2×10^{-4} or 1/4,500	1/65
Truck driving	400	10^{-4} or 1/10,000	1/222
Falls	16,339	7.7×10^{-5} or 1/13,000	1/186
Home accidents	25,000	1.2×10^{-5} or 1/83,000	1/130

NOTE: Lifetime risk based on 70-year lifetime and 45-year work exposure.

3.1.1.2 Toxic Versus Nontoxic

The term "safe" commonly means "without risk." Scientists, however, cannot ascertain conditions under which a given chemical exposure is absolutely without risk of any type. Zero risk is simply immeasurable. On the other hand, they can describe conditions under which risks are so low as to be considered of no practical consequence to a specific population. In technical terms, the safety of chemical substances - whether in food, drinking water, air, or the workplace - has typically been defined as a condition of exposure under which there is a "practical certainty" that no harm will result to exposed individuals. (As described later, these conditions usually incorporate large safety factors, so that even more intense exposures than those defined as safe may also carry extremely low risks.) Note that most "safe" exposure levels established in this way are probably risk-free, but science simply has no tools to prove the existence of essentially a negative condition.

Another fundamental concept is the classification of chemical substances as either "safe" or "unsafe" (or as **"toxic" and "nontoxic"**). This type of classification, while common even among scientists, can be highly problematic. All substances, even those that we consume in high amounts every day, can be made to produce a toxic response under some conditions of exposure. In this sense, all substances can be toxic. The important factor, then, is not simply the degree of toxicity, but rather the degree of risk; i.e., what is the probability that the toxic properties of a chemical will be realized under actual or anticipated conditions of human exposure? To answer this question requires far more extensive data and evaluation than the characterization of toxicity.[1]

[1] Some scientists will claim that carcinogens display their toxic properties under all conditions of exposure, and that there is no "safe" level of exposure to such agents. This problem receives extensive treatment later in this chapter.

3.1.1.3 Exposure and Dose

Humans can be exposed to substances in the environment through air, water, or food. Other circumstances may also provide the opportunity for exposure, such as direct contact with a sample of the substance or contact with contaminated soil. Experiments for studying the toxicity of a substance usually involve intentional administration to subjects through the diet or inhaled air, or direct application to skin. Experimental studies may include other routes of administration: injection under the skin (subcutaneous), into the blood (usually intravenous), or into body cavities (intraperitoneal).

The amount of a substance in the medium (air, diet, etc.) in which it is present or administered is the **exposure** concentration.The amount of the chemical that is received by the target, or the **dose**, may be different from the exposure amount.

The following example illustrates the difference between these two measures. Suppose a substance is present in drinking water. An individual's dose of this substance depends on the amount present in a given volume of water. For many environmental substances, this amount ranges from less than a microgram (µg) to greater than a milligram (mg). The analyst will usually report the number of mg or µg of the substance present in 1 L of water, i.e., mg/L or µg/L. These two units are sometimes expressed as parts per million (ppm) or parts per billion (ppb), respectively.[2]

Given the concentration of a substance in water (say in ppm) and the human consumption of water per unit of time, it is possible to estimate the total amount of the substance an individual will consume through water. In most public health evaluations,

[2] A liter of water weighs 1,000 g. One mg is thus one-millionth the weight of a liter of water, and 1 µg is one-billionth the weight of a liter of water.

Chapter 3

Principles of Risk Assessment

3.1 Introduction

This chapter outlines the types of scientific data needed and methods currently used to assess the human health risks of environmental chemicals. It is not intended as a complete discussion of the complex topic of risk assessment. Instead, the chapter provides a general overview of risk assessment as an introduction to the process used to determine the risks associated with chemical contamination (1).

Human health risk can be defined as the likelihood (or probability) that a given chemical exposure or series of exposures may damage the health of exposed individuals. Risk assessment involves the analysis of past chemical exposures, the adverse health effects of which may or may not have already occurred. It also involves prediction of the likely consequences of future exposures.

Risk assessment is composed of four major components : hazard identification, dose-response assessment, human exposure assessment, and risk characterization. A separate section is devoted to each component for describing the methods and tests used to gather data, the principles used for data interpretation, and the uncertainties in both the data and inferences drawn from them. Throughout these discussions, key concepts (i.e., exposure, dose, thresholds, and extrapolation) are defined and extended descriptions provided.

Many of the principles discussed in this chapter are widely accepted in the scientific community. Others, such as thresholds for carcinogens and the utility of negative epidemiological data, are controversial. In such cases, various points of view are provided, including the one most broadly adopted by public health and regulatory officials.

Finally, the concepts and principles described here, although broadly applicable, may not apply in specific cases. In some instances, the data available on a specific chemical may suggest that a general principle (e.g., that data obtained in rodent studies are generally applicable to humans) does not hold true. In such instances, the usual approach is to modify the risk assessment process to conform to the scientific finding.

3.1.1 Concepts and Definitions

3.1.1.1 Risk

Risk is the probability of injury, disease, or death under specific circumstances. It may be expressed in quantitative terms, with values from zero (expressing certainty that harm will not occur) to 1 (expressing certainty that it will). In many cases, risk can only be described qualitatively, as "high," "low," or "trivial."

All human activities carry some degree of risk. Many risks are known with a relatively high degree of accuracy because enough data have been collected on their occurrence. Table 3-1 lists the risks associated with some common activities.

The risks associated with many other activities or events, including exposure to chemical substances, cannot be readily assessed and quantified. Although considerable data have been gathered on the risks of some types of chemical exposures (i.e., the annual risk of death from intentional overdoses or accidental exposures to drugs, pesticides, and industrial chemicals), such data are generally restricted to acute poisonings. In such situations, a single, very high exposure results in an immediately observable form of injury, thus leaving little doubt about causation. Far more complex is risk assessment for chemical exposure that does not cause immediately observable forms of injury or disease (or only minor forms, such as transient eye or skin irritation). These types of exposure range from brief to extended and continuous. This chapter focuses on risk assessment for chronic, continuous exposure, although some review of acute poisoning is included.

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guidelines. Additionally, FSTRAC provides an opportunity for states to discuss their individual regulatory activities, methodology status, survey progress, and research activities and priorities.

2.5.7.2 Workshops

ODW with assistance from OTTRS is conducting a series of workshops in all EPA regions on assessing and managing drinking water contamination. The workshops are led by scientists and regulatory officials directly involved in the implementation of EPA's drinking water programs. The workshops, conducted over a period of 2 to 3 days each, stress the qualitative and quantitative risk assessment process. Additionally, presentations on the principles of pharmacokinetics, risk assessment, carcinogenicity, and toxicology are provided for the various classes of drinking water contaminants (i.e., inorganics, synthetic organics, and pesticides). The workshops focus primarily on the HA program, its development, philosophy, and methodology. Analytical technology and treatment techniques are discussed at length, as well as the communication of potential or existing health risks to the general public. Actual risk management case-studies are presented to provide hands-on experience to the attendees for specific drinking water contaminants.

2.5.7.3 Emergency Response Network

The Emergency Response Network is a long-established and important component of ODW's HA program. It is designed to give state, local, and other concerned parties rapid access to existing information on drinking water contaminants. This service is provided through a systematic access to EPA experts, databases, HAs, and other criteria and regulatory documents. Requests received by letter or telephone from the concerned party (regional and state EPA offices, state and local health departments, local water treatment facilities, or other concerned individuals or organizations) are logged in, classified, and referred to a specific chemical manager within the ODW Health Effects Branch. This staff member has ready access to other staff scientists, HAs and criteria documents, contractor support, and other national experts to formulate a response to the request. Depending on the nature of the request and the degree of urgency, the response may be relayed to the requesting party via letter, telephone, or conference call.

2.6 References

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13. Ibid., p. 25710.
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18. Ibid., p. 27486.
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Table 2-18. HAs for 50 Pesticides

Acifluorfen	Endothall
Ametryn	Fenamiphos
Ammonium sulfamate	Fluometuron
Atrazine	Fonofos
Baygon	Glyphosphate
Bentazon	Hexazinone
Bromacil	Maleic hydrazide
Butylate	MCPA
Carbaryl	Methomyl
Carboxin	Methyl parathion
Chloramben	Metolachlor
Chlorthalonil	Metribuzin
Cyanazine	Paraquat
Dalapon	Picloram
Dacthal	Prometone
Diazinon	Pronamide
Dicamba	Propachlor
1,3-Dichloropropene	Propazine
Dieldrin	Propham
Dimethrin	Simazine
Dinoseb	2,4,5-T
Diphenamid	Tebuthiuron
Disulfoton	Terbacil
Diuron	Terbufos
ETU	Trifluralin

requirements have been established for a treatment technique. Monitoring for these chemicals will help EPA to determine whether VOCs should be regulated. An additional factor that influences potential regulation is the degree of toxicity of each VOC. To define this degree of toxicity and to assist those faced with immediate VOC drinking water contamination problems, the ODW has prepared HAs for most of the chemicals listed in Table 2-9. If the toxicity data were adequate, these HAs were finalized. HAs were not finalized for many of these VOCs, since toxicity data were quite limited.

ODW is also preparing HAs for inorganics, disinfectants, and disinfection by-products. These documents will be available for review in FY 90.

2.5.6.4 *Department of the Army Munition*

EPA has entered into a Memorandum of Understanding with the Department of the Army to provide support in the preparation of HAs on various munitions chemicals having the potential to contaminate drinking water during their production, use, or disposal. Table 2-19 lists the munitions chemicals currently identified for HA development. The HAs for trinitroglycerol and nitrocellulose,TNT, HMX, RDX, and DIMP have been completed and the others are in various stages of preparation and review.

Table 2-19. Army Munition Chemicals Scheduled for Health Advisory Development

Trinitroglycerol (TNG)
Nitrocellulose (NC)
2,4,6-Trinitrotoluene (TNT)
Cyclotrimethylenetrinitramine (1-hexahydro-1,3,5-trinitro-1,3,5-triazine)(RDX)
Cyclotetramethylenetetranitramine (octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazoline) (HMX)
Diisopropyl-methylphosphate (DIMP)
Zinc chloride
White phosphorus
Hexachloroethane
Nitroguanidine
dimethylmethylophosphonate (DMMP)
1,3-Dinitrobenzene
2,4-and 2,6-Dinitrotoluene

In addition to these HAs, ODW has prepared toxicity profiles for the additional munition chemicals listed in Table 2-20. These chemicals are largely contaminants in and/or by-products of munitions manufacturing or waste disposal processes and may or may not be considered for future HAs. The toxicity profiles provide a brief survey of the properties of the chemical and the status of the toxicity database as is available from the published literature.

Table 2-20. Chemicals for Which Toxicity Profiles Have Been Prepared for the Department of the Army

1-Nitronaphthalene	1-Methyl-2-nitrobenzene
3,4-Dinitrotoluene	3,5-Dinitrotoluene
2,3-Dinitrotoluene	2,5-Dinitrotoluene
2,6-Dinitrotoluene	1-Methyl-4-nitrobenzene
1-Chloro-4-nitrobenzene	1,2-Dichloro-4-nitrobenzene

2.5.7 Other Facets of the Health Advisory Program

2.5.7.1 *Federal-State Toxicology and Regulatory Alliance Committee*

The Federal-State Toxicology and Regulatory Alliance Committee (FSTRAC) is a working group composed of EPA and state experts in the areas of risk assessment and risk management for drinking water contaminants. The goal of the committee, which meets approximately twice yearly, is to allow an exchange of information between federal and state agencies and to foster cooperation and consistency in the development of drinking water standards. Activities of the FSTRAC meetings include coordinating and updating the status of many EPA programs, including ODW drinking water regulations, HAs, NPS, and risk assessment

below) is not calculated and the DWEL is provided to give the risk manager a reference point for evaluat-ing noncarcinogenic endpoints. This infers that carcinogenicity should be considered the toxic effect of greatest concern when lifetime exposure is anticipated.

- Step 3. Lifetime HA: For noncarcinogenic chemicals the Lifetime HA is determined in Step 3 by factoring in other sources of human exposure to the chemical (e.g., air, food). Preferably, the relative source contri-bution (RSC) from drinking water is based on actual exposure data. If data are not available, a value of 20 percent is assumed for organic or inorganic chemi-cals.

These three steps can be summarized as follows:

1. Determine RfD in mg/kg/day:

$$RfD = \frac{NOAEL\ or\ LOAEL\ in\ mg/kg/day}{Uncertainty\ Factor}$$

2. Determine the DWEL in mg/L assuming 100 percent drinking water contribution:

$$DWEL = \frac{(RfD)\,(70\ kg\ for\ an\ adult)}{(2\ L/day)}$$

3. Determine Lifetime HA in mg/L:

$$\text{Lifetime HA} = \text{DWEL} \times \text{Percent drinking water contribution}$$

If the chemical is a known or probable human carcinogen, Lifetime HAs are not determined. (See Section 2.1 for a general discussion of the ODW's approach for carcinogenic effects.)

2.5.6 Health Advisory Development Status

2.5.6.1 *Completed Health Advisories*

Health Advisories for the chemicals listed in Table 2-17 have been completed and are available for use by any interested organization or individual.

2.5.6.2 *National Pesticides Survey*

The ODW has entered into a joint venture with EPA's Office of Pesticide Programs (OPP) to monitor those pesticides either known to have occurred in drinking water or most likely to be found in ground water. This joint venture is known as the National Pesticides Survey (NPS). An important element of NPS is the development of HAs for all pesticides anticipated to be detected in water samples. These HAs will allow a NPS manager to issue immediate health guidance when any pesticides are discovered in drinking water supplies. Thus, an early step in the NPS was to compile a list of chemicals to be evaluated during the sampling and analysis effort and for which HAs were needed. This list was compiled based on usage, water solubility, persistence in soil, and soil-water adsorption partition coefficient information. HAs for 50 pesticides were prepared as a part of this effort (Table 2-18).

Table 2-17. Completed Health Advisories

Acrylamide	Endrin
Alachlor	Epichlorohydrin
Aldicarb/sulfoxide/sulfone	Ethyl benzene
Arsenic*	Ethylene glycol
Atrazine	
Barium	Heptachlor/Heptachlor epoxide
Benzene	Hexachlorobenzene
Cadmium	n-Hexane
Carbofuran	Lindane
Carbon tetrachloride	Mercury
Chlorobenzene	Methoxychlor
Chromium	Methyl ethyl ketone
Cyanide	Nickel
2,4-D	Nitrate/Nitrite
DBCP	Pentachlorophenol
o,m,p-Dichlorobenzene	Styrene
1,2-Dichloroethane	Tetrachloroethylene
1,1-Dichloroethylene	Toluene
cis-1,2-Dichloroethylene	Toxaphene
trans-1,2-Dichloroethylene	1,1,1-Trichloroethane
1,2-Dichloropropane	Trichloroethylene
p-Dioxane	Vinyl chloride
Dioxin	Xylenes
EDB	
Legionella	

*Undergoing revision.

Other aspects of the NPS monitoring program already completed or nearing conclusion include development of analytical methods, selection of a hydrogeology scheme, finalization of sampling techniques, and a pilot sampling survey. This survey will ultimately involve approximately 1,500 groundwater wells, weighted toward areas of probable occurrence as influenced by pesticide usage and hydrogeology data.

2.5.6.3 *Unregulated Volatile Organic Chemicals*

Section 1445 of the SDWA directs EPA to require public drinking water systems to monitor for un-regulated volatile organic chemicals (VOCs). These are VOCs for which no primary drinking water regulations specifying a Maximum Contami-nant Level (MCL) have been developed and no

Table 2-16. Standard Assumptions Used to Develop Health Advisories

Protected Individual
One-Day HA: 10-kg child
Ten-Day HA: 10-kg child
Longer-Term: 10-kg child and 70-kg adult
Lifetime HA: 70-kg adult
Cancer risk estimates: 70-kg adult
Volume of Drinking Water Ingested/Day
10-kg child: 1 L
70-kg adult: 2 L
Relative Source Contribution
In absence of chemical-specific data: 20%
Uncertainty Factors*
10: NOAEL from human study
100: LOAEL from human study, NOAELfrom animal study
1,000:LOAEL from animal study, NOAELfrom animal study of less than lifetime duration (when calculating Lifetime HA)
10,000: LOAEL from animal study of less than lifetime duration (when calculating Lifetime HA)

*In some cases, an additional uncertainty factor of 1-10 may be used to account for scientific judgment.

Thus, derivations from these basic guidelines may be required when the total database for a specific chemical is considered.

2.5.5 Calculation of Health Advisories

As previously stated, HAs are based on identification of the adverse health effects associated with the most sensitive and meaningful noncarcinogenic endpoint of toxicity. The induction of this effect is related to both a particular exposure level and a specific period of exposure and is most often determined from the results of experimental animal studies. The general formula used to calculate HA values is as follows:

$$HA = \frac{(NOAEL\ or\ LOAEL) \times (bw)}{(UF) \times (\_\_\_\_\ L/day)}$$

$$= \_\_\_\_ mg/L\ (\_\_\_\_ \mu g/L)$$

where

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day

bw = Assumed body weight of a child (10 kg) or of an adult (70 kg)

UF = Uncertainty factor (10, 100, or 1,000)

L/day = Assumed daily water consumption of a child (1 L/day) or of an adult (2 L/day)

If the available data are derived from inhalation studies, the total exposed dose (TED) must first be determined before calculating the HA. This is accomplished by adjusting the exposure concentration for the ventilation rate and body weight of the exposed animal to achieve a dose of mg/kg bw/day.

2.5.5.1 Calculation of One-Day and Ten-Day Health Advisories

The preceding formula is used for the One-Day and Ten-Day HAs by inserting the data for a 10-kg child consuming 1 L of water per day, the appropriate UF, and the NOAEL or LOAEL derived from a study of appropriate duration.

2.5.5.2 Calculation of Longer-Term Health Advisories

Two values are calculated for the Longer-Term HA, using data for both the 10-kg child consuming 1 L per day and the 70 kg adult consuming 2 L per day along with the NOAEL and LOAEL from the study of appropriate duration. In this case, a 90-day to 1-year animal study representing approximately 10 percent of an individual's lifetime and the appropriate UF for the type of data available are employed.

2.5.5.3 Calculation of Lifetime Health Advisories

The Lifetime HA represents that portion of an individual's total lifetime exposure to the chemical that is attributable only to drinking water. All other HA values are calculated based on the assumption that drinking water is the sole source of the contaminant. The Lifetime HA is derived in a three-step process with the first two steps being mathematically equivalent to the procedure used for all other HA calculations. The third step in the calculation is added to factor in the relative contribution from other exposure sources of the chemical.

- Step 1. Reference Dose: Step 1 determines the Refer-ence Dose (RfD), formerly called the Acceptable Daily Intake (ADI) (see Section 2.1).

- Step 2. Drinking Water Equivalent Level: From the RfD, a Drinking Water Equivalent Level (DWEL) is calculated. A DWEL is defined as a medium-specific exposure level (i.e., mg/L in drinking water), as-suming 100 percent exposure from that medium, which is considered to be protective for noncarcino-genic health effects over a lifetime of exposure. The DWEL is derived by multiplying the RfD by the assumed body weight of an adult (70 kg) and then dividing by the assumed daily water consumption of an adult (2 L/day). For drinking water the DWEL is expressed in mg/L or µg/L. If the contaminant is classified as a Group A or B carcinogen, the calcula-tion is halted at this point. The Lifetime HA (Step 3

Other known criteria, guidance, or published standards are also included in the HA document as an additional means of evaluating the status of the contamination. Finally, analytical methodology and treatment technologies are included to assist the user in making the appropriate public health management decisions. Should the user require additional information, a list of the cited references is included. If the HA is based on an existing Criteria Document, it is also referenced. Additionally, the user may contact an EPA regional office as well as The Office of Drinking Water, EPA Headquarters, Washington, DC, for further assistance. Also, EPA provides a toll-free Safe Drinking Water Hotline, (800) 426-4791 or (for within area code 202) 382-5533.

2.5.3 Preferred Data for Health Advisory Development

In deriving the HA values, EPA defines specific types of data as most pertinent to each phase of the process. These data may be subdivided into three categories, as indicated in Table 2-15. The following sections explain how these data are selected to derive each of the HA values.

Table 2-15. Preferred Data for HA Development

Duration of Exposure	
One-day HA:	Up to 7 daily doses
Ten-day HA:	Up to 30 daily doses
Longer-term HA:	Subchronic study
Lifetime HA:	Chronic study Subchronic study (with added uncertainty factor)
Route of Administration	
Oral: Drinking water, gavage, or diet	
Inhalation	
Subcutaneous or intraperitoneal	
Test Species	
Human	
Appropriate animal model	
Most sensitive species	

2.5.3.1 *Duration of Exposure*

One-Day Health Advisory: The One-Day HA is calculated for a 10-kg child and assumes a single acute exposure to the chemical. It is generally derived from a study of 7 days or less.

Ten-Day Health Advisory: The Ten-Day HA, also calculated for a 10-kg child, assumes a limited exposure period of 1 to 2 weeks. It is generally derived from a study of up to 30 days duration.

Longer-Term Health Advisory: Longer-Term HAs, which are derived for both a 10-kg child and a 70-kg adult, assume a human exposure period of approximately 7 years (or 10 percent of an individual's lifetime). The longer-term HA is generally derived from a study of subchronic duration.

Lifetime Health Advisory: The Lifetime HA is derived for a 70-kg adult and assumes an exposure period over a lifetime (approximately 70 years). The Lifetime HA is generally derived from a study of chronic duration (approximately 2 years in rodents and other experimental animals), but subchronic studies may be used by adjusting the uncertainty factor employed in the calculation.

2.5.3.2 *Route of Administration*

In all cases, the route of choice is oral exposure. The preferred vehicle is drinking water, but administration via gavage or the diet is acceptable. Inhalation, subcutaneous, or intraperitoneal administration data are used on a case-by-case basis when no oral or other satisfactory data are available.

2.5.3.3 *Test Species*

The preferred species for assessing health effects is humans. However, since data in humans do not usually provide reliable dose-response information (and since very few human exposure data exist), selection of an appropriate animal model is usually required. This selection is based on the model's similarity to man in its pharmacokinetic handling of the chemical under evaluation. When different animal models vary considerably in their response to a chemical, the most sensitive, relevant species is selected. However, depending on the toxicity of the chemical and the scope of the data available, information from all sources may be used.

2.5.4 Assumptions Used in a Health Advisory

The HA values are presented under the "Quantification of Toxicological Effects" heading of the document and are based on the assumptions listed in Table 2-16.

For consistency in calculation, EPA considers the protected individual to be either a 10-kg child – the individual likely to be most adversely affected during short-term exposure periods – or a 70-kg adult. The Agency also assumes that the average drinking water intakes for a child and an adult are 1 and 2 L per day, respectively. Additionally, if actual exposure data are not available, it is assumed that drinking water accounts for 20 percent of a person's total intake of organic or inorganic chemicals. ODW uses this final assumption only when calculating the Lifetime HA, for which exposures from other sources (e.g., air or food) may be significant.

Standard uncertainty factors (UFs) are also assumed during the HA calculation (see Table 2-5). Note that the selection of UFs requires case-by-case judgments.

dermatitis and keratosis of palms and soles (and eventually skin cancer), enlargement of the liver, kidney injury, central nervous system effects, and aplastic anemia (inability to properly produce red and white blood cells).

Arsine gas, which contains arsenic, has its own distinct health effect. Exposure to this gas causes hemolysis, a bursting of the red blood cells that leads to anemia and other deleterious health effects.

4.2.1.7 Other Inorganic Ions

Fluoride in drinking water reduces dental caries (cavities) at levels of 0.7-1.2 mg/L but can discolor the teeth at levels above 2 mg/L, and can weaken bones at extremely high doses.

As mentioned earlier in the discussion of absorption, nitrates from agricultural run-off can be converted to nitrite within the GI tract. In infants, acute doses of nitrites can cause methemoglobinemia or "blue-baby" syndrome, in which the blood cannot carry oxygen to the body's tissues, resulting in possibly fatal asphyxiation and a blue cast to the skin. In adults, nitrites can combine with other compounds in the GI tract to form carcinogenic nitrosamines.

The sodium ion occurs naturally in drinking water and as a result of man's activities, such as salting icy roads in the winter. Sodium in drinking water contributes to the daily total intake of sodium, which is already high in the U.S. from consumption of salty food and is a focus of concern because of its known association with hypertension. Some epidemiological studies have shown an increased incidence of hypertension in those consuming drinking water high in sodium; other similar studies have failed to show such a correlation. It is estimated that sodium in drinking water contributes only about 10 percent to the daily total intake. As a result, some scientists suggest that sodium in drinking water is a problem mainly for those who must eat a salt-restricted diet (2).

4.2.1.8 Asbestos

Asbestos is the name of a family of fibrous minerals; the most commonly found type is called chrysotile asbestos. Most of the concern over asbestos centers on its inhalation effects: asbestosis (impaired lung function), lung cancer, and mesothelioma (cancer of the membranes lining the chest and abdomen). However, asbestos has also contaminated drinking water supplies due to mining operations, geologic erosion, degradation of asbestos cement pipes, and atmospheric sources. Research has only partially defined the health effects of ingested asbestos. Although epidemiologic studies have shown an increased incidence of GI tract cancer among those consuming water contaminated with asbestos, ingestion experiments with laboratory animals and various forms of asbestos have not revealed a reproducible, organ-specific carcinogenic effect (3).

4.2.1.9 Inorganic Radionuclides in Drinking Water

Certain unstable elements spontaneously decay into different atomic configurations, in the process releasing radiation consisting of alpha particles, beta particles, or gamma rays. These particles and rays can damage living tissue and/or cause cancer to develop, with the degree of damage depending on the type of radiation and means of exposure (i.e., inhalation, ingestion, or external radiation). As an element undergoes radioactive decay, it progresses through a series of atomic configurations, each one of which is called an isotope. Isotopes are identified by atomic weight, a number indicating the atom's number of neutral and charged particles. Everyone is exposed to some background radiation from both cosmic rays and sources on earth, such as radioactive soil and rock.

The three naturally occurring series of isotopes stem from the decay of the isotopes uranium-238, uranium-235, and thorium-232. With regard to naturally occurring radionuclides in drinking water, the uranium-238 series (for which decay isotopes include uranium-234, radium-226, and radon-222) and the thorium series (for which decay products include radium-228) are of the greatest concern. Manmade radioactive isotopes, such as strontium-90, also pose health risks, but such isotopes generally occur in lower concentrations in the environment than the naturally occurring radionuclides. However, site-specific contamination, such as leaking nuclear waste disposal sites and nuclear power plant accidents, can pose health risks due to the manmade radionuclides.

The concern over radionuclides focuses on their potential to cause cancer. In drinking water regulations, the radioactivity of an isotope is expressed in units called picocuries (pCi) that represent the isotope's number of disintegrations per second; 1 pCi is equal to 4.7×10^{10} disintegrations per second.

Radium-226 is perhaps the single most important radioactive isotope found in drinking water. It is deposited in bone and can cause bone cancer. EPA compliance data indicate that about 500 U.S. public ground-water supplies exceed the existing NIPDWR limit for combined radium-226 and radium-228 of 5 pCi/L. However, many exceeded the limit only slightly. Radium-228 is also a bone- seeking carcinogen.

The most commonly found forms of natural uranium are uranium-234 and uranium-238. Natural uranium is also believed to cause bone cancer;

where a concentration above 200 µg cadmium per gram of tissue damages the organ.

The kidney injury is thought to be responsible for the brittle bones and pain described above. Through inhalation, cadmium can cause chronic obstructive pulmonary disease and emphysema. Although cadmium has been established as a probable human carcinogen (Class B1) through inhalation, ingested cadmium has not been shown to be carcinogenic (Class D for ingestion). Cadmium has also been associated with high blood pressure in humans and laboratory animals.

4.2.1.4 Iron

Iron in drinking water can result from naturally occurring iron in the soil and from corrosive water contacting iron water piping. Chronic iron toxicity is not a significant problem with regard to drinking water. However, iron-rich water can discolor clothes. Acute iron toxicity, on the other hand, is a major problem in that children often mistake iron supplements for candy and accidentally consume large amounts of iron. Such accidental ingestion can cause GI tract problems, metabolic acidosis, and cardiovascular collapse.

4.2.1.5 Other Metals

There are many other metals that can be found in drinking water. Many of these metals (for example, copper, zinc, chromium, cobalt, manganese, and the nonmetal selenium) are considered essential minerals in the diet. Although potentially harmful to health in very high doses (such as high occupational doses or site-specific situations such as mine leachate), these metals are not considered a major health hazard in drinking water. Further, many foods contain significant amounts of metals, far overshadowing the contribution from drinking water in terms of the total dose. It is important to note, however, that a certain subpopulation of people are unusually sensitive to copper (i.e., Wilson's disease).

Some metals, such as zinc, copper, and manganese, in the amounts usually found in drinking water generally present only the same type of relatively minor problem that iron does, i.e., staining and objectionable taste. Silver produces "cosmetic" effects like skin discoloration at the higher observed drinking water levels. Others have (or may have) chronic toxicities similar to the metals described in the previous section, but occur very rarely in drinking water and only exert a toxic effect at extremely high levels. Such metals may also occur in drinking water in a less harmful form than in occupational or medical exposures.

For example, nickel in occupational exposures has been shown to increase the risk of lung and nasal-cavity cancer but is not considered a drinking water problem because its occurrence in drinking water is rare and its absorption through food and drinking water intake is low. Other inorganics in this category would include antimony, barium, beryllium, phosphorus, and trivalent chromium. However, in certain parts of the U.S., metals not occurring in high levels in other areas have been a drinking water problem. For example, in northern Illinois high levels of barium in groundwater have required treatment because of possible GI and cardiovascular effects. In some areas, selenium contamination has required treatment because of possible GI effects at lower doses and liver damage at very high doses.

Other metals require further study. For example, aluminum is generally considered to have a low order of toxicity. As a result, aluminum is purposefully used in water treatment, and many people consume antacid medicines composed of aluminum hydroxide without experiencing ill health effects. However, aluminum may be associated with neuropsychiatric disorders in patients receiving renal dialysis who also receive aluminum as part of their therapy. Also, laboratory animals exposed to aluminum have shown growths called neurofibrils that have also been seen in people suffering from Alzheimer's disease.

4.2.1.6 Arsenic

Arsenic occurs naturally in bedrock and soil and is a waste product from the manufacture of products such as pesticides and from smelting operations. Arsenic is considered an essential dietary element, although in very small amounts. There are four main types of arsenic: organoarsenicals, pentavalent arsenic, trivalent arsenic, and arsine gas.

Arsenic can be excreted relatively quickly; its half-life is 2 days. Arsenic has a wide variety of chronic toxic effects, but many of them stem from its ability to increase the permeability of capillaries in various locations in the body. This increased permeability allows plasma to leak into the tissues, for example, leading to severe diarrhea and kidney injury. (In the past, women took arsenic to obtain a "milk and roses" complexion; the arsenic broke capillaries in the cheeks, creating a rosy complexion.) Arsenic damages the central nervous system by inflaming peripheral nerves and causing brain injuries, and the liver by fatty infiltration and tissue necrosis. Also, EPA has classified arsenic as a Type A human carcinogen (human carcinogen based on epidemiological studies), with skin and lung cancer as the two principal types of cancer arising from arsenic exposure.

Early signs of chronic arsenic poisoning include diarrhea; skin pigmentation and texture changes; edema of eyelids, face, and ankles; and a garlic odor of the breath. As exposure continues, symptoms include

as a B(2) substance, a probable human carcinogen based on sufficient evidence from animal studies and insufficient evidence from humans. Lead's reproductive hazards have long been known since in the past it was used to induce abortions.

The more subtle, long-term effects of lead are the subject of much scientific interest. Some research has suggested that subtle developmental problems in children, such as learning disabilities, may be linked to long-term, low-level exposure to lead both in childhood and the prenatal stage.

In the diagnosis of lead poisoning, specific concentrations of lead in the blood (μg lead/g blood) correlate with specific symptoms. X-rays of long bones also aid diagnosis by indicating the degree of exposure. The presence of compounds called heme precursors in the urine indicates that lead exposure has interfered with the synthesis of the heme portion of hemoglobin.

Finally, lead can also exist in organolead compounds. Here, the symptoms are different than described above. The central nervous system again is the main target, but the symptoms are primarily neuropsychiatric, including insomnia, nightmares, irritability, and anxiety.

4.2.1.2 Mercury

In terms of toxicologic effects, mercury can be divided into three types: elemental mercury (such as in thermometers and other measuring devices); inorganic mercury salts (used in products such as skin cream, antiseptics, and diuretics); and organomercurials (used in fungicides for grain).

Elemental mercury is not significantly absorbed through the GI tract when it is consumed orally and thus is, in this instance, essentially nontoxic. However, elemental mercury as a vapor can be readily absorbed through the lung, where it can enter the bloodstream and subsequently the brain. Also, elemental mercury released into the ocean is converted into the more harmful methylmercury by plankton, which are then consumed by fish.

The inorganic mercury salts, because they are ionized and water soluble, do not readily pass membranes in the body. Thus, these compounds do not readily pass the blood/brain or placental barriers and only about 10 percent of a given dose is absorbed through the GI tract. The organomercurials, because they are lipid soluble, readily pass membranes in the body. Thus, these compounds readily pass through the blood/brain and placental barriers and about 90 percent of a given dose is absorbed through the GI tract. The half-life for both inorganic mercury salts and organomercurials is about two months.

Acute mercury poisoning, common before World War II, when many nonprescription medicines contained mercury, is relatively rare today. Of more importance for drinking water is chronic, long-term mercury poisoning. Chronic exposure to vapor from elemental mercury produces neuropsychiatric symptoms, including depression, irritability, shyness, insomnia, emotional instability, forgetfulness, confusion, excessive perspiration, uncontrolled blushing (erethism), and tremors. Less is known about the effects of chronic exposure to inorganic mercury salts, although the kidney has been identified as the target organ of toxicity. Chronic exposure to methylmercury (from grain and through the food chain) affects the central nervous system but affects the senses rather than emotions, as with elemental mercury vapors. Effects include abnormal tingling sensations, constriction of the visual field, hearing defects, speech impairment, and ataxia (impaired muscle coordination). Mercury is a teratogen and the fetus is extremely susceptible to methylmercury. (A well-known case of mercury poisoning in Minimata Bay, Japan resulted in birth defects and widespread illness in 1968.) EPA has given mercury a Class D carcinogenicity designation: i.e., inadequate evidence of carcinogenicity from animal data.

In the diagnosis of mercury poisoning, the various neuropsychiatric symptoms may be difficult to detect. Often family members will note a pronounced change in a relative's behavior. To reveal elevated blood mercury levels, tests can be performed on blood and urine, as well as hair, which also concentrates mercury.

4.2.1.3 Cadmium

Cadmium has several sources or uses. It is a by-product of lead and zinc mining; is used as a pigment and in corrosion-resistant coatings and nickel-cadmium batteries; and is released when fossil fuels are burned. It can also enter drinking water when corrosive water contacts certain types of water piping. Cadmium's health effects were made public by an incident in Japan in which rice paddies were contaminated with cadmium-rich zinc mine drainage. Rice grown on the paddies concentrated the cadmium and those eating it suffered easily broken bones and extreme joint pain; thus, acute cadmium poisoning was referred to as Itai-Itai (ouch-ouch) disease.

Since cadmium is water soluble, only 1-5 percent of a given dose is absorbed in the GI tract (although 10-40 percent can be absorbed through the lung). Cadmium distributes to the kidney and liver. Unlike the previously discussed metals, cadmium has an extremely long half-life of 10-30 years. Acute cadmium poisoning causes GI disturbances. Chronic cadmium poisoning affects the kidney the most,

When considering metabolism, researchers also look at species, strain, and gender differences. In laboratory animals, these species, strain, and gender differences can play an important role in the animal's ability to metabolize a chemical; in humans, these factors are less significant. However, age is an important factor in both humans and laboratory animals, with both the very young and very old more susceptible to certain chemicals. Also, exposure to certain chemicals can induce the production of the enzyme P-450 and similar enzymes (for example, phenobarbital, DDT, and dioxin for P-450), resulting in a higher level of that enzyme in the body compared to the general population.

4.2 Toxicology of Selected Substances

The following sections provide a general overview of the toxicology of certain substances. This overview focuses on health effects due to exposure to or consumption of drinking water, as opposed to effects from occupational exposure or air pollution. The omission of a substance does not imply that exposure to it in any setting is safe. Further, although some substances have been identified by both chemical and trade names, space will not permit listing all of the trade names for commercially produced toxic substances such as pesticides. Wherever possible, toxic chemicals have been grouped according to chemical structure.

For some of the following substances, an EPA carcinogenicity class designation has been provided; Table 4-1 summarizes EPA's carcinogenicity rating system.

Table 4-1. EPA's Carcinogenicity Rating System

Class Designation	Definition
A	Human carcinogen based on sufficient epidemiological evidence
B	Probable human carcinogen based on at least limited evidence of carcinogenicity to humans (B1), or usually a combination of sufficient evidence in animals and inadequate data in humans (B2)
C	Possible human carcinogen based on limited evidence of carcinogenicity in animals in the absence of human data
D	Not classified based on inadequate evidence of carcinogenicity from animal data
E	No evidence of carcinogenicity for humans (no evidence of carcinogenicity in at least two adequate animal tests in different species or in both epidemiological and animal studies)

4.2.1 Inorganics

Described below are the health effects of lead, mercury, cadmium, other metals, arsenic, inorganic ions (fluoride, nitrate, and sodium), asbestos, and inorganics such as radionuclides.

4.2.1.1 Lead

Lead in drinking water comes from several sources, including lead materials in water piping; food; tetraethyl lead in gasoline (which ends up in the air, soil, and water); lead-based paint (pre-WW II paint); improperly glazed earthenware; and occupational sources such as smelters and lead-acid battery manufacturing. Drinking water risk assessors must consider the total dose of lead from all these sources, not only from drinking water. For drinking water, the most significant source of lead is lead solder and piping in water distribution systems, particularly when contacted by corrosive water. While the use of lead solder and piping in repairs and construction of water piping has been banned (SDWA Amendments of 1986), much of the existing water distribution system still contains lead materials.

Since lead is a water-soluble compound, it is relatively poorly absorbed; in adults, only about 10 percent of the lead ingested through the GI tract is absorbed into the bloodstream. Lead is initially distributed to the kidney and liver and then redistributed mostly to the bone (about 95 percent), where it is visible in x-rays. Lead does not readily enter the central nervous system in adults because the blood/brain barrier can keep it out. However, in children, the blood/brain barrier is not as developed; such exposure in children can affect their mental development.

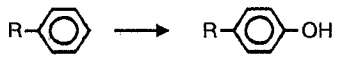
Acute lead poisoning is rare. Instead, chronic lead poisoning or "plumbism" is the effect of most interest to risk assessors. An important chronic effect, although not the most serious, is a GI tract condition known as lead colic. This condition is more common in adults and can be quite painful. Because of the pain, lead colic often causes an exposed person to seek medical help, thus discovering the lead exposure before more serious problems can develop. Lead can also affect the neuromuscular system by decreasing muscle tone in the wrists and feet. This condition, "lead palsy," was common among house painters before World War II. The most serious effects of lead are called lead encephalopathies. These effects are more common in children and can be quite serious; approximately 25 percent of children with lead encephalopathies die and approximately 40 percent of the survivors experience neurologic after-effects.

Exposure to lead also affects the body's blood-forming system. Lead can interfere with the synthesis of heme (part of the oxygen-carrying compound hemoglobin); can cause anemia; and can damage red blood cells in a condition known as basophilic stippling. Effects on the kidney include injury and cancer in laboratory animals. As a result, lead has been classified by EPA

Figure 4.2. Several types of chemical reactions occurring in metabolism (1)

Examples of the general type of oxidation reactions catalyzed by the cytochrome P-450-containing mono-oxygenases:

- Aromatic hydroxylation



- Aliphatic hydroxylation $RCH_2CH_2CH_3 \longrightarrow RCH_2CHOHCH_3$

- N, O, and S-Dealkylation $R\text{-}(\overset{H}{N}, O, S)\text{-}CH_3 \longrightarrow R(RNH_2, OH, SH)$

- Epoxidation $R\text{-}CH=CHR' \longrightarrow R\text{-}\overset{O}{\overset{/\ \backslash}{CH\text{-}CH}}\text{-}R'$

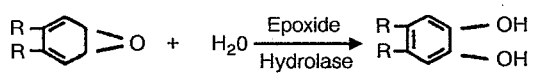
- Desulfuration $R_1R_2\overset{S}{\overset{\|}{P}}\text{-}X \longrightarrow R_1R_2\overset{O}{\overset{\|}{P}}\text{-}X + S$

- Sulfoxidation $RSR_1 \longrightarrow R\text{-}\overset{O}{\overset{\|}{S}}\text{-}R_1$

- N-Hydroxylation $RNH\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 \longrightarrow R\text{-}NOH\overset{O}{\overset{\|}{C}}CH_3$

Non P-450:

- Epoxide hydrolase (closely associated with P-450)



- Esterases and amidases

$$\underset{\text{Ethyl Acetate}}{CH_3\overset{O}{\overset{\|}{C}}\text{-}OC_2H_5} \longrightarrow \underset{\text{Acetic Acid}}{CH_3\overset{O}{\overset{\|}{C}}OH} + \underset{\text{Ethanol}}{CH_3CH_2OH}$$

- Alcohol and aldehyde dehydrogenase

$$CH_3CH_2OH + NAD^+ \longrightarrow \underset{\text{Acetaldehyde}}{CH_3\overset{O}{\overset{\|}{C}}H} \longrightarrow \underset{\text{Acetate}}{CH_3\overset{O}{\overset{\|}{C}}OH}$$

Several of the reactions do not involve P-450, but rather rely on enzymes such as amine oxidase, epoxide hydrolase, esterases, amidases, and alcohol and aldehyde dehydrogenase (see Figure 4-2) . The alcohol dehydrogenase reaction serves well to explain metabolism. If we could not metabolize alcohol and relied on our kidneys and lungs to eliminate it without metabolism, we would remain intoxicated for months after drinking alcohol.

The Phase II reactions add various specialized molecules to compounds to make them water soluble. For instance, the body can add a glucuronic acid molecule (similar to a sugar molecule, which has several hydroxyl groups). Other Phase II reactions add a tripeptide called glutathione (consisting of glycine, cysteine, and glutamic acid) to create a compound that is further metabolized and then excreted. Still others add a sulfate to make a compound more water soluble. There are also several other types of Phase II reactions, but they play a less important role in the metabolism of toxicants and thus will not be described here.

possible through the hair follicles, through the cells of the sweat glands and sebaceous glands, and through cuts or abrasions (which increase the rate and degree of absorption). The sole means of absorption through the skin appears to be passive diffusion. The dermis is much more permeable than the epidermis.

4.1.2 Distribution

Distribution of toxicants to various organs depends on the ease with which it crosses cell membranes, its affinity for various tissues, and the blood flow through the organ. A toxicant's site of concentration is not necessarily the target organ of toxicity. For example, many lipid-soluble toxicants (such as the chlorinated hydrocarbon insecticides) are stored in fat, where they cause relatively little harm, and lead can be harmlessly stored in bone. However, a contaminant stored in fat can be released back into the bloodstream during conditions such as starvation, dieting, or illness when fat is consumed.

A number of anatomical barriers in the body are thought to prevent or hinder the entrance of certain toxicants into organs. The so called blood/brain barrier does not prevent toxicants from entering the central nervous system (CNS); rather, the physiologic conditions at the blood/brain interface make it more difficult for some toxicants to leave the blood and enter the CNS. In general, lipid-soluble toxicants can cross the blood/brain barrier but some water-soluble toxicants cannot. Even less of a barrier is the "placental barrier"; simply stated, any chemical absorbed into the mother's bloodstream will cross her placenta and enter the bloodstream of the fetus to some degree.

4.1.3 Excretion

Chemicals can be excreted from the body in several ways, but the two most important routes with regard to drinking water are through the kidney and through the biliary system (liver). The kidney removes toxicants from the blood in the same way that the endproducts of metabolism are eliminated i.e., glomerular filtration, passive tubular diffusion, and active secretion. Glomerular filtration simply involves filtering of compounds below a certain molecular weight (and thus size) through pores in a part of the kidney referred to as the glomeruli. In this way, the kidney acts as a filter for the blood, with the heart providing the pumping power to move the blood through the porous membrane. All toxicants with a molecular weight less than 60,000 will filter through the glomeruli unless they are bound to plasma proteins (only a few do so). Most toxicants in drinking water have a molecular weight of between 100 and 500 and thus easily pass through the glomeruli. The toxicants then pass through collecting ducts and tubules where, if they are lipid-soluble, they can defeat the excretion process by moving (by passive diffusion) through the tubule wall and back into the bloodstream. In contrast, water-soluble compounds continue on and are excreted through the urine. The kidney also employs "carrier" processes to actively transport some toxicants into the urine.

The liver eliminates toxicants from the body through the bile, which passes into the intestine through the gall bladder and bile duct, and finally out of the body via the feces. As in the kidney, the transport mechanisms used are passive diffusion and carrier-mediated transport. Toxicants that have been excreted into the intestine through the bile can be reabsorbed (especially if they are lipid-soluble) into the bloodstream while in the intestine. This reabsorption process is called enterohepatic circulation.

Toxicants are also excreted through several other routes, including the lungs, GI tract, cerebrospinal fluid, milk, sweat, and saliva. Of these, only milk is significant for drinking water contaminants. Because milk has a relatively high concentration of fat (3.5 percent), lipid-soluble compounds such as DDT and PCBs can concentrate in it. Also, because milk is slightly acidic (with a pH of 6.5), basic compounds may concentrate in it. In this way, toxicants may be passed from mother to child or from cows to humans.

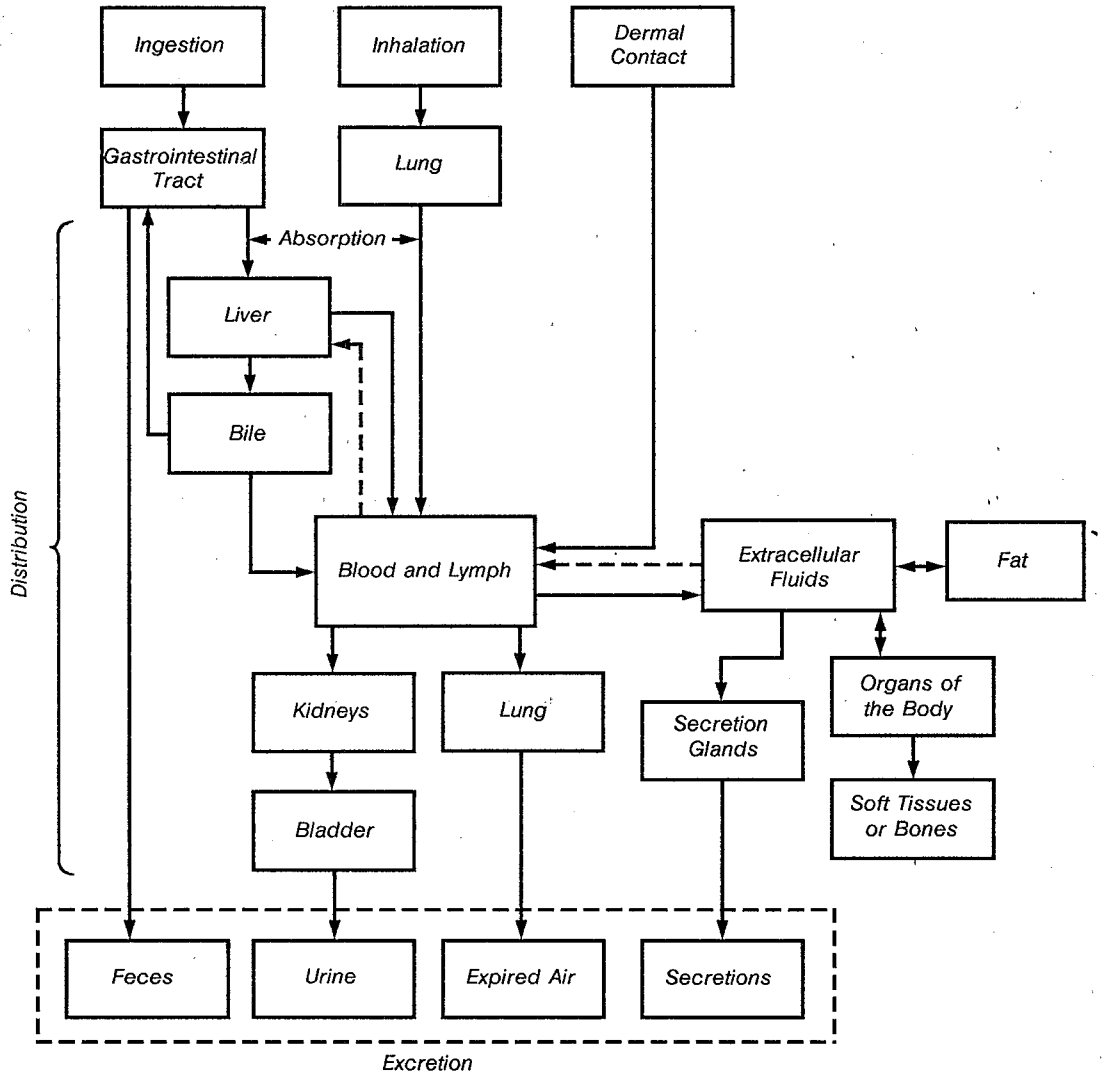
An important concept in excretion is a toxicant's half-life, which is the time it takes for one-half of the chemical to be eliminated from the body. Thus, if an imaginary chemical A has a half-life of 1 day, 50 percent of it will remain within the body 1 day after absorption. Two days after absorption, 25 percent will remain; at 3 days, 12.5 percent will remain, and so on.

4.1.4 Metabolism

Because lipid-soluble compounds are reabsorbed in the kidney and intestine due to their ability to cross cell membranes, the body metabolizes these toxicants into water-soluble compounds, which can be excreted easily. However, in some instances, metabolism of a chemical creates a more toxic chemical or does not change the chemical's toxicity.

Two types of reactions occur in metabolism: relatively simple Phase I reactions (oxidation, reduction, and hydrolysis) and more complex Phase II reactions (conjugation and synthesis). All of these reactions occur primarily in the liver. Oxidation is the mechanism of metabolism for many compounds. An important family of enzymes in oxidation is the P-450 mono-oxygenases. Figure 4-2 illustrates several types of oxidation reactions catalyzed by cytochrome P-450 mono-oxygenases; such reactions create water soluble compounds.

Figure 4-1. Key routes of chemical absorption, distribution, and excretion.



methemoglobinemia or "blue-,baby syndrome." Also, nitrates in the GI tract of people of all ages may lead to the formation of carcinogenic compounds called nitrosamines.

Age is also an important factor affecting the intestine's ability to act as a barrier to certain toxicants. For example, lead is absorbed to a much greater extent in newborns than in adults.

Even though a chemical has been absorbed through the GI tract, it can still be excreted or metabolized by the intestine or liver before it reaches the systemic circulation. This first chance to eliminate the chemical is known as the first-pass effect.

Drinking water pollutants can also enter the body through the lung—for example, when volatile organic compounds volatilize in a warm shower. For some chemicals, such as the VOCs, absorption through the lungs can be considerable.

The lungs are anatomically designed to absorb and excrete chemicals, as is shown by the absorption of oxygen and excretion of carbon dioxide. The alveoli have a large surface area (50-100 m^2), are supplied with a high flow of blood, and the blood is very close (10 µm) to the air space within the alveoli. Toxicants may have to pass through as few as two cells to travel from the air into the bloodstream.

The skin is relatively impermeable to toxicants : This barrier is over 100 cells thick. However, some toxicants, such as carbon tetrachloride, can be absorbed through the skin in sufficient quantities to cause liver injury. Absorption through the skin is

Chapter 4

Principles of Toxicology

In order to familiarize the drinking water risk assessor with the basic physiology on which toxicology is based, this chapter begins by describing the absorption, distribution, excretion, and metabolism of toxic substances. Then, the toxicology of four broad categories of substances—inorganics, pesticides, solvents and vapors, and other synthetic compounds—is reviewed.

4.1 Absorption, Distribution, Excretion, and Metabolism of Toxic Substances

The body's response to a toxic chemical depends on the dose administered. However, once a toxicant enters the body, the interplay of four processes—absorption, distribution, excretion, and metabolism—determines the actual effect of a toxic chemical on the "target organ," which is the organ that can be damaged by that particular chemical. For example, carbon tetrachloride affects the liver and benzene affects the hematopoietic (blood-cell forming) system. Figure 4-1 summarizes routes of absorption, distribution, and excretion.

4.1.1 Absorption

Understanding absorption requires a review of the two main mechanisms by which toxicants pass through membranes within the body: passive transport (simple diffusion and filtration) and active transport (assisted chemical transport). Simple diffusion—movement from an area of higher to lower concentration—accounts for much of the transport of chemicals within the body. Lipid-soluble compounds, especially nonionized forms, readily diffuse through the lipid part of cell membranes. Filtration can be defined as the flow of a solute through pores in a membrane. It comes into play in the kidney, where these pores are relatively large, thus allowing excretion of chemicals through the urinary tract. Active transport involves certain carrier compounds that move chemicals from areas of low concentration to high concentration. (For more detail on active transport, see Section 4.1.3.)

Absorption of toxicants across body membranes and into the bloodstream can occur in the gastrointestinal (GI) tract, lungs, and through the skin. For drinking water, the GI tract is the key portal of entry. Most chemicals, once they enter the GI tract, must be absorbed to exert their toxic effect. Lipid-soluble, nonionized compounds such as DDT and PCBs are more readily absorbed by diffusion in the GI tract than lipid-insoluble, ionized compounds such as lead and cadmium. The GI tract also employs specialized active transport systems for compounds such as sugars, amino acids, pyrimidines, calcium, and sodium; in general, these active transport systems do not play a major role in absorption of toxicants. (Some toxicants, however, can be absorbed in the GI tract through active transport systems; for example, lead can be absorbed through calcium's transport system and thallium through iron's transport system.)

The effect of digestive fluids must be considered when examining toxicants in the GI tract. For example, a toxin like snake venom is nontoxic when administered orally because it is a protein that stomach enzymes break down into amino acids, much in the same way that a hamburger is digested. In newborns, the GI tract has a higher pH and a higher number of *E. coli* bacteria than in adults. These conditions convert nitrate, a common drinking water pollutant from agricultural run-off, into the more toxic chemical, nitrite. The nitrite then interferes with the blood's ability to carry oxygen, thus causing

is not to specify an RfD, but to ascertain risk. There are no means available to accomplish this for noncarcinogens. The MOE is used as a surrogate for risk; as the MOE becomes larger, the risk becomes smaller. At some point, most scientists agree that the MOE is so large that human health is almost certainly not jeopardized. The magnitude of the MOE needed to achieve this condition will vary among different substances, but its selection would be based on factors similar to those used to select safety factors to establish RfDs.

The risk characterization process can result in very different statements of risk. As shown in Table 3-9, risk characterization for an imaginary Chemical A produces three distinct statements. The first statement indicates that 327 per 1 million exposed people will die, using three significant digits to estimate the risk outcome. The second statement more cautiously gives only a range of people that will die – 100 to 1,000 people per 1 million people exposed. Finally, the third statement can only suggest that an assumption that the chemical in question is carcinogenic to humans is prudent.

Table 3-9. Three Different Statements Resulting from the Same Risk Characterization Process

--	327 per 1,000,000 exposed people will die from lifetime exposure to Chemical A.
--	Chemical A is carcinogenic in rats and mice. Application of low-dose extrapolation models and human exposure estimates suggests that the range of risks in humans is 100-1,000 deaths per 1,000,000 persons exposed.
--	Chemical A is carcinogenic in rats and mice and it is prudent public health policy to assume it is also carcinogenic in humans.

3.6 References

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8. Ibid.

After the known or expected human dose is estimated, carcinogenic risk can be characterized. Although the models in use yield a wide range of dose-response relationships for the same data, the projections of the more protective models are not likely to underestimate risk, at least to experimental animals. (They may strongly overestimate it.) In a few cases, dose-response data are available from human epidemiological studies and may be used in lieu of animal data for low-dose extrapolation.

Certain classes of carcinogens do not apparently possess the capacity to damage DNA (i.e., they are not genotoxic). Some scientists maintain that such nongenotoxic carcinogens must operate under threshold mechanisms. Many of the reasons for such a hypothesis are sound, but no general consensus has yet emerged on this matter. It is nevertheless possible that some classes of carcinogens could be treated in the same way as noncarcinogens for purposes of establishing RFDs.

3.4 Human Exposure Assessment

Assessment of human exposure requires estimation of the number of people exposed and the magnitude, duration, and timing of their exposure. The assessment could include past exposures, current exposures, or exposures anticipated in the future. In some cases, measuring human exposure directly, either by measuring levels of the hazardous agents in the ambient environment or by using personal monitors, is fairly straightforward. In most cases, however, detailed knowledge is required of the factors that control human exposure, including those factors that determine the behavior of the agent after its release into the environment. The following types of information are required for this type of exposure assessment:

- The factors controlling the production of the hazardous agent and its release into the environment
- The quantities of the agent released, and the location and timing of release
- The factors controlling the fate of the agent in the environment after release, including its movement, persistence, and degradation (degradation products may be more or less toxic than the original agent)
- Human contact with the agent, including the size and distribution of vulnerable human populations, and activities that facilitate or prevent contact
- Information on human intakes

The amount of information available varies greatly from case to case. For some agents, fairly detailed information is available on the sources of release into the environment and on the factors controlling the quantities released. However, for many agents little information is available on the factors controlling dispersion and fate after release. Measurements of transport and degradation in the complex natural environment are often difficult to conduct; thus, it is more common to rely on mathematical models of the key physical and chemical processes, supplemented with experimental studies conducted under simplified conditions. Such models have been developed in considerable detail for radioisotopes, but have not yet been developed in comparable detail for other physical and chemical agents.

In comparison with toxicology and epidemiology, the science of exposure assessment is still at a very early stage of development. Except in fortunate circumstances, in which the behavior of an agent in the environment is unusually simple, uncertainties arising in exposure assessments are often at least as large as those arising in assessments of inherent toxicity.

Once these various factors are known, human data can be estimated, as described earlier. The dose, its duration and timing, and the nature and size of the population receiving it are the critical measures of exposure for risk characterization.

3.5 Risk Characterization

The final step in risk assessment combines the information gained and analysis performed during the first three stages to determine the likelihood that humans will experience any of the various forms of toxicity associated with a substance. Risk is generally characterized as follows:

1. For noncarcinogens and for the noncarcinogenic effects of carcinogens, the margin-of-exposure (MOE) is estimated by dividing the experi-mental NOAEL by the estimated exposure dose.

2. For carcinogens, risk is estimated at the human dose by multiplying the actual human dose by the risk per unit of dose projected from the dose-response modeling. A range of risks might be produced, using different models and assumptions about dose-response curves and the relative susceptibilities of humans and animals.

Although risk characterization can be far more complex than is indicated here (especially if problems of timing and duration of exposure are introduced), the MOE and the carcinogenic risk are the ultimate measures of the likelihood of human injury or disease from a given exposure or range of exposures. RfDs are not measures of risk; they are derived by imposing a specified safety factor (or, in the above language, a specified MOE). The purpose of risk characterization

Table 3-8. Lifetime Risks Derived from Different Extrapolation Models (8)

Model Applied	Lifetime Risk (1.0 mg/kg/day)
One-hit	6.0×10^{-5} (1 in 17,000)
Multistage	6.0×10^{-6} (1 in 167,000)
Multihit	4.4×10^{-7} (1 in 2.3 million)
Weibull	1.7×10^{-8} (1 in 59 million)
Probit	1.9×10^{-10} (1 in 5.3 billion)

NOTE: All risks are for a full lifetime of daily exposure. The lifetime is used as the unit of risk measurement because the experimental data reflect the risk experienced by animals over their full lifetimes. The values shown are upper confidence limits on risk.

be consistent with the data. In many cases, however, such data are very limited, resulting in great uncertainty in how to select a model for low-dose extrapolation. At present, understanding of the mechanism of carcinogenesis is still quite limited. Biological evidence, however, does indicate a linearity of tumor initiation, and consequently linear models are frequently used by regulatory agencies.

The one-hit model always yields the highest estimate of low-dose risk. This model is based on the biological theory that a single "hit" of some minimum critical amount of a carcinogen at a cellular target – namely, DNA – can initiate an irreversible series of events that eventually lead to a tumor.

EPA generally uses the linearized multistage model for low-dose extrapolation because it usually yields estimates of risk that are the most conservative, representing a plausible upper limit for the risk. In other words, the actual risk is unlikely to be higher than the risk predicted under this model.

The probit model incorporates the assumption that each individual in a population has a "tolerance" dose and that these doses are distributed in the population in a specified way. The other models (Weibull, multihit, and logit) have more complex bases and are not widely used. None of these models currently incorporates a threshold dose for an exposed population.

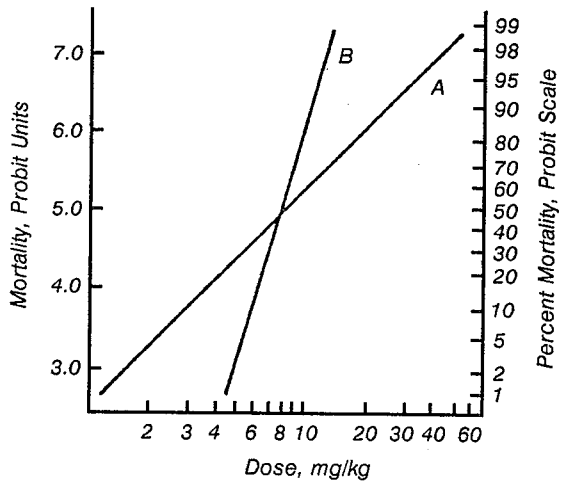
3.3.2.3 Slope of the Dose-Response

The toxicologist must also keep in mind the slope of the dose-response. In Figure 3-2, dose-responses for the imaginary chemicals A and B are shown. Note that, although both chemicals have the same LD_{50}, the values for higher and lower doses differ greatly.

3.3.2.4 Interspecies Extrapolation

For the majority of agents, dose-response evaluation primarily involves the analysis of tests that were performed on laboratory animals. In extrapolating

Figure 3-2 Slope of the dose-response.



the results of these animal tests to humans, the doses administered to animals must be adjusted to account for differences in size and metabolic rate. Differences in metabolism may influence the validity of these extrapolations if, for example, the actual material producing the carcinogenic effect is a metabolite of the tested chemical, and the animal species tested and humans differ significantly in their metabolism of the material.

Several methods have been developed to adjust the doses used in animal tests to allow for differences in size and metabolism. They assume that human and animal risks are equivalent when doses are measured in:

- mg/kg body weight per body
- mg/m^3 of body surface area per day
- parts per million in the air, water, or diet
- mg/kg per lifetime

Currently, a scientific basis for using one of the above extrapolation methods over another has not been established.

3.3.3 Dose-Response Assessment: A Summary

For substances that do not display carcinogenic properties, or for the noncarcinogenic effects of carcinogens, dose-response evaluation consists of describing observed dose-response relationships and identifying experimental NOAELs. NOAELs can be used to establish RFDs, or can be used for the type of risk characterization described in Section 3.5.

For carcinogens, various models are applied to project the dose-response curve from the range of observed dose-responses to the range of expected human doses.

3.3.2.2 *Potency and High-to-Low Dose Extrapolation*

Table 3-7 illustrates the need for high-to-low dose extrapolation. Assume that a substance has been tested in mice and rats of both sexes and has been found to produce liver cancer in male rats. A typical summary of the data from such an experiment might be as follows:

Table 3-7. Incidence and Probability of Liver Cancer at Low and High Doses (7)

Lifetime Daily Dose (mg/kg/day)	Lifetime Incidence of Liver Cancer in Rats	Lifetime Probability of Liver Cancer
0	0/50	0.0
125	0/50	0.0
250	10/50	0.20
500	25/50	0.50
1,000	40/50	0.80

The incidence of liver cancer is expressed as a fraction, and is the number of animals found to have liver tumors divided by the total number of animals at risk. The probability (P) of cancer is simply the fraction expressed as a decimal (i.e., 25/50 = 0.50).

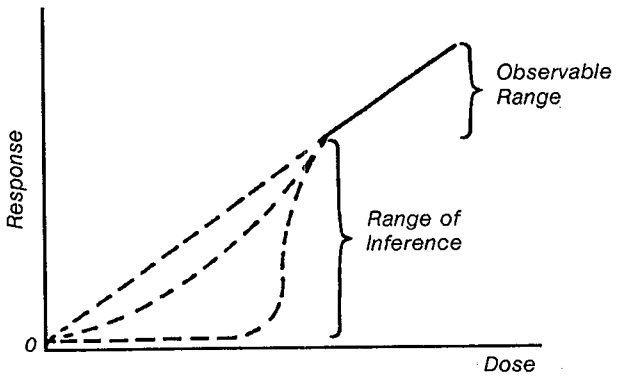
Although there is no effect at 125 mg/kg/day, the response is nevertheless compatible with a risk of about 0.05 (5 percent) because of the statistical uncertainties associated with the small numbers of animals used.

This experiment reveals that if humans and rats are about equally susceptible to the agent, an exposure of 250 mg/kg/day in humans will increase their lifetime risk by 20 percent; if 1,000 people were to be exposed to this substance at this dose for a lifetime, then 200 of these people will be expected to develop cancer. This is an extremely high risk and obviously one that few people would sanction. However, it is near the low end of the range of risks that can be detected in animal experiments.

To continue with the illustration, assume that the estimated daily dose of the chemical in the human population is 1.0 mg/kg/day. It thus becomes of interest to know the risk to male rats at 1.0 mg/kg/day.

However, a great difference lies between the doses used experimentally (125 - 1,000 mg/kg/day) and the dose of interest (1.0 mg/kg/day). Figure 3-1 illustrates the difference between the dose-response observed in experiments and the dose-response of ultimate interest to toxicologists. The risks that would exist at a dose of 1.0 mg/kg/day are quite small and to determine whether they exist at all would require enormous numbers of animals (perhaps hundreds of thousands). In these circumstances, scientists must rely on something other than experimentation to estimate potential risk – i.e., mathematical models to estimate low-dose risks from high-dose risks.

Figure 3-1. Dose-response observable in experiments and range of inference for dose-response at low doses .



Such models describe the expected quantitative relationship between risk (P) and dose (d), and are used to estimate a value for P at the dose of interest (in our example, the dose of 1.0 mg/kg/day). The accuracy of the projected P at d is a function of how accurately the mathematical model describes the true, but practically immeasurable, relationship between dose and risk at the low dose levels.

Various models may lead to very different estimations of risk. None is chemical-specific; that is, each is based on general theories of carcinogenesis rather than on data for a specific chemical. None can be proved or disproved by current scientific data, although future results of research may increase our understanding of carcinogenesis and help refine these models. Regulatory agencies currently use one-hit, multistage, and probit models, but regulatory decisions are usually based on results of the one-hit or multistage models. They also use multihit, Weibull, and logit models for risk assessment.

If several of these models are applied to the hypothetical liver cancer data, several different estimates of lifetime risk for male rats at the dose of 1.0 mg/kg/day can be derived (see Table 3-8). No experimental basis is available for deciding which estimate is closest to the truth. Nevertheless, it is possible to show that the true risk is very unlikely to be higher than the risk predicted by the various models.

In cases in which relevant data exist on biological mechanisms of action, the selection of a model should

general population versus populations such as workers expected to exhibit a narrower range of susceptibilities). Safety factors of 10, 100, 1,000, and 10,000 have been used in various circumstances.

NOAELs are used to calculate the reference dose (RfD, formerly called Acceptable Daily Intake, ADI) for humans for chemical exposures. The RfD is derived by dividing the experimental NOAEL, in mg/kg/day for the toxic effect appearing at lowest dose, by one of the safety factors listed above. The RfD (or its equivalent) is thus expressed in mg/kg/day. For example, a substance with a NOAEL from a chronic toxicity study of 100 mg/kg/day may be assigned an RfD of 1 mg/kg/day for chronic human exposure.

This approach has been used for several decades by EPA and other federal regulatory agencies such as the Food and Drug Administration, as well as by such international bodies as the World Health Organization and by various committees of the National Academy of Sciences.

Although some biological justification can be found for using safety factors to protect the more sensitive members of the human population, scientific support for the specific safety factors used is limited. However, evaluation of interspecies and intraspecies variability data indicates that the current approach is protective.

There is no way to ensure that exposures at RfDs estimated in this fashion are without risk. The RfD represents an acceptable, low level of risk but not a guarantee of safety. Conversely, there may be a range of exposures well above the RfD, perhaps including the experimental NOAEL itself, that bears no risk to humans. The "NOAEL-safety factor" approach includes no attempt to ascertain how risk changes below the range of experimentally observed dose-response relations.

3.3.2 Effects That May Not Exhibit Thresholds

At present, only agents displaying carcinogenic properties are treated as if they do not display thresholds (although a few scientists suggest that some teratogens and mutagens may behave similarly). In more technical terms, the dose-response curve for carcinogens in the human population achieves zero risk only at zero dose; as the dose increases above zero, the risk immediately becomes finite and thereafter increases as a function of dose. Risk in this case is the probability of producing cancer, and at very low doses the risk can be extremely small (this will vary according to the potency of the carcinogen).

3.3.2.1 The Carcinogenic Process

Cancer can be defined as an uncontrolled new growth of cells, or "neoplasm," with a tendency to be invasive and metastasize (or spread). In some cases, neoplasms can also be benign, or slow to develop, noninvasive, and local. The type of carcinogenesis depends on the type of cell involved: Carcinomas are malignant growths of epithelial cells; lymphomas are usually malignant neoplasms in lymph tissue; sarcomas are malignant neoplasms in bone, muscle, or other connective tissue; and leukemias are malignant growths of cells in blood-forming tissues.

By one theory of chemical carcinogenesis, the condition proceeds in two stages: initiation (irreversible cell damage) and promotion (development of a neoplasm in tissue in which initiation has already occurred) (1). Initiation can occur and not immediate-ly proceed to cancer because of the body's ability to repair or suppress the carcinogenic process. Initiators are referred to as genotoxic carcinogens because they bind to the genetic DNA. Primary genotoxic carcinogens act directly on the DNA, while secondary carcinogens must be metabolized to another form to exert their genotoxic effect.

Other cancer-causing agents - epigenetic carcinogens - do not act directly on the DNA. These substances can act by promoting a genotoxic effect or through various other mechanisms. For example, inhaled asbestos fibers cause cancer through a solid-state epigenetic effect, in which the physical nature of the asbestos fibers contacting lung and other tissues causes cancer. Other epigenetic carcinogens include hormones (which only cause cancer in high doses), immunosuppressive agents, and cocarcinogens (which increase the carcinogenicity of a genotoxic agent when administered with it). Some carcinogens appear capable only of initiating the process and thus are termed "initiators." Others called promoters act only at later stages, and some carcinogens may act at several stages.

Some scientists postulate that a very small amount of a carcinogen, even a single molecule, can affect the transition of normal cells to cancerous cells at one or more of the various stages, and that a greater amount of the carcinogen merely increases the probability that a given transition will occur. Under these circumstances, an absolute threshold below which there is no effect on the process (even though the effect may be exceedingly small) is extremely unlikely.

This theory of the carcinogenic process is still under extensive scientific scrutiny and is by no means established, though it has substantial support in the scientific community. The "multistage" model, as the theory is called, has influenced the development of some of the models used for dose-response evaluation. Before describing these models, the experimental dose-response information obtained from bioassays and the need for models of the dose-response relationship must be discussed.

When humans are exposed to two or more chemicals, several results may occur. The chemicals may act independently; that is, exposure to the additional chemical(s) has no observable effect on the toxic properties of the first chemical. Or, toxic effects of chemicals may be additive; that is, if chemical A produces 1 unit of disease and chemical B produces 2 units of disease, then exposure to chemicals A and B produces 3 units of disease. Exposure to combinations of chemicals may also produce a greater- than-additive or synergistic effect; that is, exposure to chemicals A and B produces more than 3 units of disease. Chemicals can act as potentiators, in which exposure to chemical A normally produces no disease but greatly increases the effect of chemical B. Ethyl alcohol (and other forms of alcohol) and carbon tetrachloride are examples of such substances. (When carbon tetrachloride was used widely as a stain remover, those using it with hangovers - i. e., high blood ethyl alcohol levels - sometimes suffered severe liver damage.) Finally, chemicals may reduce the degree of toxicity of each other (antagonism); that is, exposure to chemicals A and B produces less than 3 units of disease. Hazard evaluation of such mixtures of chemicals is complex and not standardized.

3.2.4 Hazard Identification: A Summary

For some substances, the available database includes substantial information on effects in humans and experimental animals, as well as information on the biological mechanisms underlying the production of one or more forms of toxicity. In other cases, the database is highly limited and includes only a few studies in experimental animals.

In some cases, all the available data may point in a single direction, leaving little ambiguity about the nature of the toxicity associated with a given compound; in others, the data may include apparently conflicting sets of experimental or epidemiological findings. It is not unusual for toxicity tests to show conflicting results on well-studied compounds. If the tests were performed properly, positive test results usually outweigh negative test results. Confusion may be compounded by the observation that the type, severity, or site of toxicity may vary with the species of animal exposed. Although results in animals are and have been useful in predicting effects in humans, such notable exceptions as the testing on thalidomide have occurred. (Premarket testing of thalidomide on animals did not reveal its teratogenic effects in humans.) This complex issue, briefly mentioned here, must be considered for each compound examined.

A proper hazard evaluation should include a critical review of each pertinent data set and of the total database bearing on toxicity. It should also include an evaluation of the inferences about toxicity in human populations who might be exposed. At this stage of risk assessment, however, there is no attempt to project human risk. To do so, at least two additional sets of analyses must be conducted: the dose-response assessment and the human exposure assessment.

3.3 Dose-Response Assessment

The next step in risk assessment describes the relationship between the amount of exposure to a substance and the extent of toxic injury or disease. Even where good epidemiological studies have been conducted, reliable quantitative data on exposure in humans are rarely available. Thus, in most cases, dose-response relationships must be estimated from studies in animals, which immediately raises three serious problems: 1) animals are usually exposed at high doses, and effects at low doses must be predicted by using theories about the form of the dose-response relationship; 2) animals and humans often differ in susceptibility (if only because of differences in size and metabolism); and 3) the human population is heterogeneous, so some individuals are likely to be more susceptible than average.

Toxicologists conventionally make two general assumptions about the form of dose-response relationships at low doses: for effects that involve alteration of genetic material (including the initiation of cancer) and for most other biological effects. These assumptions are discussed in the following subsections.

3.3.1 Threshold Effects

Commonly accepted theory suggests that most biological effects of noncarcinogenic chemical substances occur only after a threshold dose is achieved. In the experimental systems described here, the threshold dose is approximated by the NOAEL.

Another widely accepted premise, at least in the setting of public health standards, is that the human population is likely to have much more variable responses to toxic agents than the small groups of well-controlled, genetically homogenous animals ordinarily used in experiments. Moreover, the NOAEL is itself subject to some uncertainty since, for example, epidemiologists may not be sure that the most serious effects of a substance have been identified. For these reasons, standard-setting and public health agencies divide experimental NOAELs by large "safety factors" when examining substances that display threshold effects. The magnitude of safety factors varies according to the following: the nature and quality of the data from which the NOAEL is derived; the seriousness of the toxic effects; the type of protection being sought (protection against acute, subchronic, or chronic exposures); and the nature of the population to be protected (i.e., the

3.2.2 Human Studies

Information on adverse health effects in human populations is obtained from four major sources: 1) summaries of self-reported symptoms in exposed persons; 2) case reports prepared by medical personnel; 3) correlation studies (in which differences in disease rates in human populations are associated with differences in environmental conditions); and 4) epidemiological studies. The first three types of studies can be characterized as descriptive epidemiology. Epidemiological studies compare the health status of a group of persons who have been exposed to a suspected agent with that of a comparable nonexposed group. Although they cannot identify a cause-and-effect relationship, they can draw attention to previously unsuspected problems and can generate hypotheses that can be further tested.

Most epidemiological studies are either case-control studies or cohort studies. Case-control studies identify a group of individuals with a specific disease and attempt to ascertain commonalities in exposures the group may have experienced in the past. The carcinogenic properties of DES, a drug once used to prevent miscarriages, were discovered through such studies. Cohort studies examine the health status of individuals known to have had a common exposure to determine whether any specific condition or cause of death is revealed to be excessive compared to an appropriately matched control population. Benzene leukemogenesis was established with studies of this type. Generally, epidemiologists have turned to occupational settings or to patients treated with certain drugs to conduct their studies.

Convincing results from epidemiological investigations can be enormously beneficial because the data provide information about humans under actual conditions of exposure to a specific agent. Therefore, results from well-designed, properly controlled studies are usually given more weight than results from animal studies. Although no study can provide complete assurance that a chemical is harmless, negative data from epidemiological studies of sufficient size can assist in establishing the maximum level of risk due to exposure to the agent.

Interpreting epidemiological results, however, can be quite difficult. These points should be remembered:

- Appropriately matched control groups are difficult to identify, because the factors that lead to the exposure of the study group (e.g., occupa-tion or residence) are often associated with other factors that affect health status (e.g., lifestyle and socioeconomic status).
- Controlling for related risk factors (i.e., cigarette smoking) that have strong effects on health is difficult.
- Few types of health effects other than death are recorded systematically in human populations, and even the information on cause of death is of limited reliability. For example, infertility, miscarriages, and mental illness are not as a rule systematically recorded by public health agencies.
- Accurate data on the degree of exposure to potentially hazardous substances are rarely available, especially when exposures have taken place in the past. Establishing dose- response relationships is thus frequently impossible.
- When investigating diseases that take many years to develop, such as cancer, epidemiologists must wait many years to ascertain the absence of an effect. Of course, exposure to suspect agents could continue during these extended periods of time and thereby further increase risk.
- The statistical detection power of epidemiological studies depends on the use of very large populations.

For these reasons, interpretations of epidemiological studies are sometimes subject to extreme uncertainties. Independent confirmatory evidence is usually necessary, such as supporting results from a second epidemiological study or supporting data from experimental studies in animals.

Negative findings in epidemiological studies must also be interpreted with caution. For example, suppose a drinking water contaminant causes cancer in one out of every 100 people exposed to 10 units. The average time required for cancer to develop from 10 units of exposure is 30 years (not uncommon for a carcinogen). After people have been exposed to the drinking water contaminant for 15 years, an epidemiologist decides to study its effects. He locates the death certificates of 20 people exposed to the contaminant, but finds little information on their actual exposure. Some were exposed when the contaminant first entered the water supply, others several years later. The health records, which are incomplete, reveal no excess cancer in the 20 people when compared to an appropriate control group. Is it then correct to conclude that the carcinogen is not carcinogenic?

3.2.3 Chemical Interactions

The foregoing discussion of hazard evaluation was predicated on exposure to a single toxic agent. Humans are rarely exposed to only one substance, however: commercial chemicals contain impurities; chemicals are used in combinations; and lifestyle choices (e.g., smoking, drinking) may increase exposure to mixtures of chemicals.

3.2.1.6 Categorizing Toxic Effects

Toxicity tests may reveal that a substance produces either a wide or narrow variety of adverse effects on different organs or systems of the body. Some effects may occur only at the higher doses used, while only the most sensitive indicators of a substance's toxicity may occur at the lower doses.

The toxic characteristics of a substance are usually categorized according to the organs or systems that they affect (e.g., liver, kidney, nervous system) or the diseases they cause (e.g., cancer, birth defects). (See Chapter 4 for descriptions of toxic effects on various organs and systems.)

Although uncertainties are associated with most evaluations of animal toxicity data, special problems arise with interpreting carcinogenicity data. These problems are the source of much controversy, as described in the rest of this section.

One area of uncertainty and controversy concerns the occurrence of certain types of tumors in control animals. In most animal experiments, control animals also develop tumors, and interpreting the results of such experiments requires comparing the incidence of tumors in control animals with that observed in treated animals. This comparison is not always straightforward. For example, the lifetime incidence of lung tumors in a certain strain of male mice, untreated with any substance, may vary from a low of about 2 percent to a high of about 40 percent; the average rate is about 14 percent. Suppose that these male mice treated with a substance exhibited a 35 percent incidence of lung tumors, and control animals exhibited an incidence of 8 percent. Because the initial analysis of these data showed that the treated animals experienced a statistically significant increase in tumor incidence, the substance producing this effect was labeled a lung carcinogen.

However, further analysis of the data took the investigators to a different conclusion. The 35 percent incidence observed in the exposed animals was within the range of tumor incidence that is normally experienced by male mice (i.e., from 2 to 40 percent), and the particular group of male mice used as controls in this experiment also exhibited an incidence within the range, although at the low end. Therefore, use of the simple statistical test of significance was claimed to have erroneously led to the labeling of the substance as a carcinogen.

Another major area of uncertainty lies in the interpretation of experimental observations of benign tumors. Some types of tumors are clearly malignant; that is, they are groups of cells that grow in uncontrolled ways, invade other tissues, and are frequently fatal. No significant controversy surrounds such tumors, and pathologists generally agree that their presence is a clear sign that a carcinogenic process has occurred. Other tumors are benign at the time they are observed by pathologists, and whether they should be considered indicators of a carcinogenic process is not always clear. Some tumors will remain benign for the lifetime of the animal, but others will progress to malignancy. Generally, when establishing the total tumor incidence, scientists combine the number of animals with benign tumors that are thought to be part of the carcinogenic process with the number with malignancies. Many pathologists disagree with this approach. The issue has been especially controversial in connection with tumors found in rodent livers.

3.2.1.7 Using Short-Term Tests for Carcinogens

The lifetime animal study is the primary method used for detecting the carcinogenic properties of a substance. In recent years, however, short-term experimental techniques have become available.

Short-term tests for carcinogenicity measure effects that empirically or theoretically appear to be correlated with carcinogenic activity. These tests include assays for gene mutations in bacteria, yeast, fungi, insects, and mammalian cells; mammalian cell transformation assays; assays for DNA damage and repair; and in vitro assays (outside the animal) and in vivo assays (within the animal) for chromosomal mutations in animal cells. In addition to these rapid tests, several tests of intermediate duration involving whole animals have been used. These include the induction of skin and lung tumors in female mice, breast cancer in certain species of female rats, and anatomical changes in the livers of rodents.

Other tests are used to determine whether a substance will interact with the genetic apparatus of the cell, as some well-known carcinogens apparently do. However, not all substances that interact with DNA have been found to be carcinogenic in animal systems. Furthermore, not all animal carcinogens interact directly with genetic material.

These short-term tests are playing an increasingly important role in helping to identify suspected carcinogens. They provide useful information in a relatively short period, and may become critical screening tools, particularly for selecting chemicals for long- term animal tests. They may also assist in understanding the biological processes that underlie the production of tumors. However, they have not been definitely correlated with results in animal models. Regulatory agencies and other public health institutions do not consider positive or negative results in these test, as definitive indicators of carcinogenicity or the lack thereof, but only as ancillary evidence.

Table 3-5. Typical Costs of Descriptive Toxicity Tests (1988) (5)

Test	Cost, $
Acute oral toxicity	2,000
Acute dermal toxicity	2,800
Acute inhalation toxicity	3,300
Acute dermal irritation	700
Acute eye irritation	450
Skin sensitization:	
Draize test	6,700
FCAT (Freunds Complete Adjuvant Test)	3,900
Guinea pig maximization test	5,500
Split adjuvant test	3,200
Buehler test	3,500
Open epicutaneous test	3,200
Mauer optimization test	3,850
Repeated dose toxicity (oral gavage):	
14-day exposure	10,200
28-day exposure	12,800
Genetic toxicity tests:	
Reverse mutation assay (*S. typhimurium*)	1,000
Mammalian bone marrow cytogenics (in vivo)	13,000
Micronucleus test	2,000
Dominant lethal test	8,500
Host mediated assay	4,400
Drosophila	12,500
Subchronic mouse study (90 days)	65-75,000
Rat oncogenicity	1,000,000
Mouse oncogenicity	1,000,000
Reproduction	200,000
Teratology (2 species	45,000
Acute toxicity in fish (LC_{50})	1,250
Daphnia reproduction study	1,400
Algae growth inhibition	1,450

NOTE: The number of animals used for various types of tests varies, as does the duration of the tests. See Table 3-4 for details.

Table 3-6. Typical Observations for a Subchronic or Chronic Toxicity Test (6)

Mortality
Body weight changes
Diet consumption
Urinalysis: color, specific gravity, pH, albumin, sugar, leukocytes, erythrocytes, epithelial cells, case, bacteria, crystals
Hematology: RBC, WBC, platelets, differential
Clinical chemistry: glucose, creatinine, BUN, uric acid, sodium, potassium, CO_2, chloride, calcium, phosphorus, cholesterol, triglycerides, bilirubin, SGOT, SPGT, lactate dehydrogenase, alkaline phosphate, iron, total protein, albumin, globulin.
Gross and microscopic examination: brain, heart, liver, kidney, spleen. testes, thyroid, adrenal (and weigh the eight aforementioned organs), aorta, bone, bone marrow smears, gall bladder, esophagus, duodenum, jejunum, cecum, colon, lung, lymph node, sciatic nerve, parathyroid, pituitary, salivary gland, epididymis, prostate.

Program) use a definition of MTD that does not take biological mechanisms into account.

3.2.1.5 *Conducting and Interpreting Toxicity Tests*

To ensure the utility of results of toxicity tests, the following questions must be asked (1):

1. Was the experimental design adequate to test the hypothesis under examination?
2. Was the general conduct of the test in compliance with standards of good laboratory practice?
3. Was the dose of test compound correctly determined by chemical analysis?
4. Was the test compound adequately characterized with regard to the nature and extent of impurities?
5. Did the animals actually receive the test compound?
6. Were animals that died during the test adequately examined?
7. How carefully were test animals observed during the conduct of the test?
8. What tests were performed on the animals (i.e., blood tests, clinical chemistry tests) and were they adequately performed?
9. If the animals were examined histopathologically (i.e., detailed pathological examination based on sections taken from individual tissues), was the examination performed by a qualified pathologist?
10. Was the extent of animal and animal tissue examination adequate?
11. Were the various sets of clinical and pathology data properly tabulated (i.e., tumors grouped in accordance with NTP guidelines)?
12. Were the appropriate statistical tests used and were they adequately performed?
13. Was the report of the test sufficiently detailed so that these questions can be answered?

A proper evaluation would ensure that these types of questions were examined and would include a list of qualifications on test results in areas where answers were missing or unsatisfactory.

Table 3-4. (continued)

Fertility and Reproductive (Phase I)	Teratogenic (Phase II)	Perinatal and Postnatal (Phase III)	Multi-Generation Reproductive	Mutagenic
• Rats usually used • Typical protocol: - 2 or 3 doses that produce no maternal toxicity - Male is given the chemical 60-80 days prior to mating and female at 14 days prior - 25 rats per dose • Typical observations: - Percent pregnant - Number of still-born - Weight, growth, survival, and general condition of offspring during first 3 weeks of life	• Rats (25 per dose) and rabbits (20 per dose) used • Typical protocol: - Exposed during organogenesis (days 6-15 in rats); equivalent to human first trimester - Fetuses removed by cesarean section 2 or 3 days before normal delivery • Typical observations: - Number of live, dead, and re-sorbed fetuses - Fetuses weighed, measured and examined grossly - Histological and skeletal examination	• Administer chemical in rats from day 15 of gestation throughout delivery and lactation • Observe birthweight, survival, and growth of offspring during first 3 weeks of life	• Rats used (25 female and 25 male) • Typical protocol: - First generation (FO) exposed from 40 days of age until breeding at day 140; F1 thus exposed in utero and during breeding and development of F2 - 3 dose levels • Typical observations: - Gross necropsy and histopathology - Number of pregnancies, stillborn, livebirths, and other reproductive indices	• Study of ability to change genetic material in nucleus of cell • Tests used include: - Cytogenic analysis of bone marrow - Dominant lethal test in rodents; exposed male mated with untreated female - Salmonella reverse mutation (Ames) with metabolic activation

In an experiment of this size, assuming none of the control animals develop tumors, the lowest incidence of cancer that is detectable with statistical reliability is in the range of 5 percent, or 3 out of 60 animals developing tumors. If control animals develop tumors (as they frequently do), the lowest range of cancer incidence detectability is even higher. A cancer incidence of 5 percent is very high, yet ordinary experimental studies are not capable of detecting lower rates and most are even less sensitive.

Advocates of using the MTD argue that inclusion of high doses will compensate for the weak detection power of these experiments. By using the MTD, the toxicologist hopes to elicit any important toxic effects of a substance and ensure that even weak carcinogenic effects of the chemical will be detected. Critics of the MTD do not reject the notion that animal experiments may be statistically insensitive, but rather are concerned about the biological implications of such high doses. Their concerns can be summarized as follows:

- The underlying biological mechanisms that lead to the production of cancer may change as the dose of the carcinogen changes.
- Current methods for estimating an MTD for use in an experiment do not usually take such biological mechanisms into account.
- The biological mechanisms at work under conditions of actual human exposure may be quite different from those at work at or near the MTD.

In general, observations at or near an MTD (as determined by current methods) thus may not be qualitatively relevant to conditions of actual human exposure.

Many risk assessors agree that greater attention should be paid to developing data on the underlying mechanisms of carcinogenicity and their relation to dose. Also, a range of doses should be included in carcinogenicity testing to assess whether physiological mechanisms that would normally detoxify the chemical are overwhelmed at an MTD. These biological considerations have considerable merit, but are frequently disregarded in designing studies and interpreting data. Although some risk assessors have attempted to develop a more biologically relevant definition of MTD, most current tests (those carried out by the National Toxicology

Table 5-8. Carbon Usage Rates for Several Organics

Type	Usage Rate lb/MG
Volatile Organics	
TCE	200
PCE	70
Vinyl chloride	NA
Cis-1,2-dichloroethylene	250
Pesticides	
Aldicarb	25
Chlordane	5
DBCP	15
Chlorinated Aromatics	
PCB	5
Dichlorobenzene	10

To obtain carbon usage rates, tests can be performed in the laboratory or in the field. Laboratory tests include isotherm and minicolumn tests. The isotherm test employs the following equation, called the Freundlich isotherm relationship:

$$x/m = k\,c^{1/n} \qquad (5\text{-}1)$$

where

x/m = equilibrium capacity (mg contaminant/g carbon)

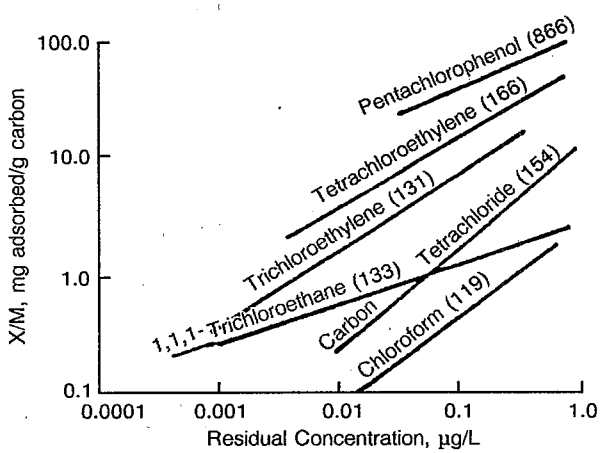
k = capacity at 1 mg/L contaminant concentration

c = contaminant effluent concentration (mg/L

1/n = exponent

This equation can be plotted to obtain "isotherms" that provide an indication of which compounds are more adsorbable than others. Isotherms also provide a rough estimate of the carbon usage rate. Figure 5-13 provides isotherms for several compounds. The compounds with a higher molecular weight, such as pentachlorophenol, are more adsorbable and less likely to break through; i.e., appear in the effluent-treated water. The isotherm test also provides information for gauging competitive effects of other contaminants, comparative performance of different carbons, and the effects of changing temperature and pH. Isotherm tests can be performed relatively quickly and cost approximately $1,000 - $3,000 per test. Further, published isotherm data for many contaminants are available (7).

Figure 5-13. Adsorption isotherms for several organic compounds found in ground-water supplies.



Numbers in parentheses indicate the molecular weight of the compound.

In contrast, "dynamic column" field tests can cost tens of thousands of dollars and can take 6-10 months before breakthrough is achieved. These tests allow many variables to be changed and provide accurate information on carbon depth, loading rate, and usage rate.

Between the isotherm test and dynamic column tests, in terms of cost and complexity, is the "minicolumn" laboratory test. This test uses a device that simulates a GAC system on a small scale, incorporating raw water storage; stainless steel and teflon tubing and fittings to avoid contamination of the sample; and a small tube of carbon through which a contaminated sample is passed. This system is comparable to the isotherm test in cost and duration (not including equipment costs) but provides more information. Further, the carbon usage rates obtained with the minicolumn test are relatively accurate (more accurate than isotherm tests, but less accurate than field studies).

The contaminant concentrations and type of contaminants both affect the carbon life. Figure 5-14 illustrates the relationship between carbon life and influent concentration at three different desired effluent concentrations for the contaminant trichloroethylene. Note that, to bring an influent concentration of 200 µg /L down to 1 µg/L, the carbon life would be about 3 months; while at a higher influent concentration, such as 500 µg/L, the carbon life drops to 2 months.

Figure 5-15 illustrates the relationship between influent concentration and carbon life at an effluent concentration of 10 µg /L. Note that for the three contaminants shown, the carbon life at an influent concentration of 200 µg/L would be about 1 month for

Figure 5-12. The granular activated carbon adsorption process.

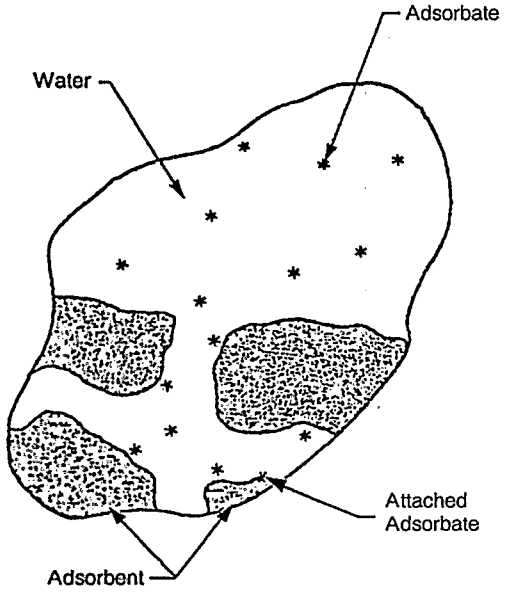


Table 5-7. Readily and Poorly Adsorbed Organics

Readily Adsorbed Organics
•Aromatic solvents (benzene, toluene, nitrobenzenes)
•Chlorinated aromatics (PCBs, chlorobenzenes, chloronapthalene)
•Phenol and chlorophenols
•Polynuclear aromatics (acenapthene, benzopyrenes
•Pesticides and herdicides (DDT, aldrin, chlodane, heptachlor)
•Chlorinated nonaromatics (carbon tetrachloride, chloroalkyl ethers)
•High MW hydrocarbons (dyes, gasoline, amines, humics)
Poorly Adsorbed Organics
•Alcohols
•Low MW ketones, acids, and aldyhydes
•Sugars and starches
•Very High MW or colloidal organics
•Low MW aliphatics

increases adsorbability by increasing the overall driving force for adsorption in that solution.

Fortunately, most of the common organic drinking water contaminants are easily adsorbed by GAC (i.e., PCBs, benzene, toluene, carbon tetrachloride, trichloroethylene) and those that are less easily adsorbed (i.e., aldehydes and ketones) are less commonly found in drinking water. When ozone treatment is applied ahead of GAC, the ozone can break down the more easily adsorbed compounds into less easily adsorbed compounds.

The solution itself is also a factor to consider. The pH of the solution can have an impact if organic acids and bases are being removed; however, many of the organic drinking water contaminants are neutral compounds. Increased solution temperature can reduce adsorption somewhat. Probably the biggest impact of the solution is the presence of competing contaminants. For example, naturally occurring organics (represented by total organic carbon) can compete for carbon sites with the contaminants. This competition reduces the total capacity of carbon available for the contaminant.

There are two forms of activated carbon: granular and powdered activated carbon. The granular form is used in a filtering mode in that water is passed through a closed vessel in which contaminants are adsorbed onto the carbon. Powdered activated carbon (PAC) is simply pulverized granular activated carbon that is added to water along with a coagulant. The organic contaminants are adsorbed onto the PAC and the carbon then settles out in a sedimentation basin or clarifier.

5.3.1.2 Process Design Considerations

Important process design considerations include the contaminants present, the EBCT, the carbon usage rate, surface loading rate, and carbon depth.

The EBCT is the primary factor in determining the size and capital cost of a system. The EBCT can range from 5-30 minutes, although studies have shown that times less than about 7.5 minutes usually do not obtain good use of the carbon. Generally, EBCTs of 10-15 minutes are used for the organics typically found in drinking water. In the case of removing radon, however, an EBCT of 180-200 minutes must be used to achieve removals of 95% or greater. While such a long EBCT might be feasible for point-of-use applications, it would drive up the cost of GAC treatment for larger applications.

The carbon usage rate determines the operating cost. Generally, 100-300 lb of carbon is used per million gallons of water treated for the types of organics found in ground-water supplies. However, some of the synthetic organic chemicals now under consideration for EPA regulation have lower usage rates of about 50 lb per million gallons. Table 5-8 shows usage rates for three categories of contaminants: VOCs, pesticides, and chlorinated aromatics. These usage rates translate into replacement intervals, at normal demand, for VOCs of about 3 to 6 months, and for the other two categories, 1 to 2 years.

Figure 5-11. Activated alumina system: operating mode flow schematics.

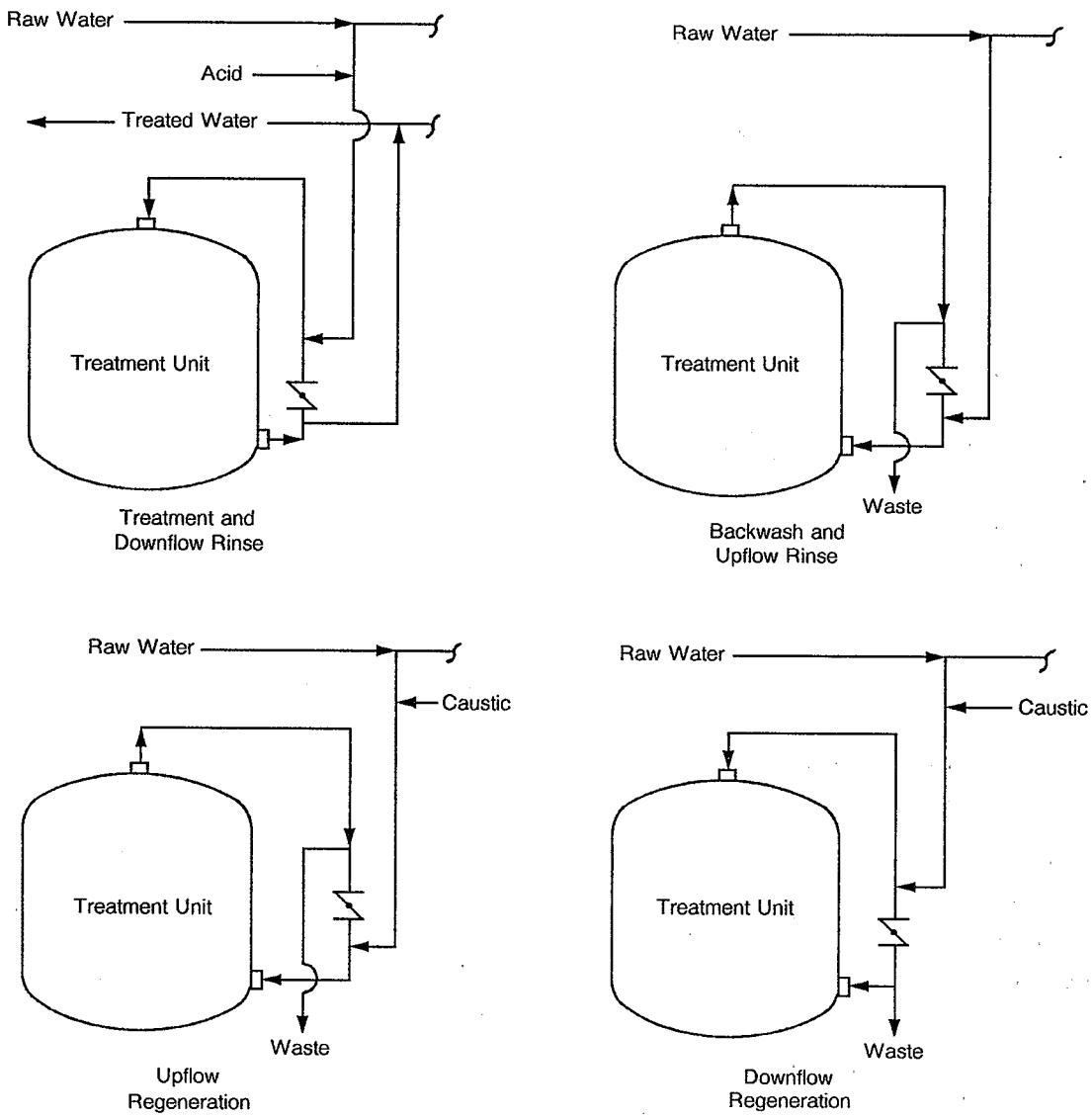


Table 5-6. Removals Possible with Activated Alumina

>90 Percent Removal	>70 Percent Removal
As (V)	Se (VI)
F	
Se (IV)	

area due to its high porosity. In fact, 1 gram of GAC has about the surface area of a football field. Also important is the reversibility of the adsorption force. Since this force is mostly physical and partly electrical in origin, it can be easily reversed (unlike chemical reactions), thus allowing the contaminants to be driven off the carbon to allow re-use. (It is important to remember that regular charcoal is not activated carbon and does not have activated carbon's large internal surface area.)

Several factors affect the degree of success possible with the adsorption process. First, the nature of the contaminant itself is important. Compounds with a branch-chained molecular structure are generally more adsorbable than straight-chained compounds. Compounds with higher molecular weights are more adsorbable than those with low molecular weights. Less polar compounds like PCE are generally better adsorbed than more polar compounds like alcohols and ketones. Table 5-7 lists both readily adsorbed and poorly adsorbed organic compounds. A higher concentration of the contaminant in the solution also

presaturated with hydroxyl ions through a strong sodium hydroxide solution. In the activated alumina process, the anions of fluoride, arsenic, and selenium are exchanged for hydroxyl ions on the surface of the alumina. When the alumina is completely saturated with contaminant ions, it must be regenerated with the sodium hydroxide solution. Because the regeneration process increases the pH of the water within the unit, it must be neutralized with a 3-percent sulfuric acid solution. Figure 5-11 illustrates an activated alumina treatment system in four basic operating modes.

Like the standard ion exchange technique, activated alumina requires pretreatment to remove suspended solids, although a high concentration of total dissolved solids (and even some suspended solids) can be tolerated. Competing ions are also an important process design consideration.

This process is most effective for removal of arsenic, fluoride, and selenium. It is not effective for removal of barium, radium, or cadmium. Table 5-6 summarizes the removal percentages possible with activated alumina.

Advantages of the activated alumina process include relative insensitivity to flow and thus on-demand operation; high tolerance for total dissolved solids; and effective removal of arsenic, selenium, and fluoride.

A significant disadvantage is the necessity of using caustic acid and base solutions, which present a hazard to operators. Also, sodium hydroxide must be liquefied in heating units, even in warm climates. The activated alumina process is slower than other ion exchange processes; activated alumina has an EBCT of about 5 minutes compared to about 2-3 minutes for other ion exchange processes. Further adding to the cost is the fact that the sodium hydroxide solution dissolves the activated alumina medium; a typical unit might lose 20 percent of the medium per year. Finally, the wastestream from the regenerant will be high in contaminants and aluminum, and thus must be disposed of properly.

5.2.4.1 Case Study: Activated Alumina

This case study describes the use of activated alumina for fluoride removal from a ground-water supply in Gila Bend, AZ (4,5,6). Raw water fluoride levels ranged from 4 to 6 mg/L. The plant had a capacity of 600 gpm (900 gpm max.) and included activated alumina, caustic regeneration, acid neutralization, and an evaporation pond for regenerant waste treatment.

Fluoride levels achieved in the treated water averaged approximately 1 mg/L.

5.2.5 Treatment Technologies for Radionuclides

Treatment techniques usually used for inorganics, and some techniques used for organics, can be used to treat radionuclides (see Sections 5.2 or 5.3 for more information).

Methods shown in the literature to be effective for treatment of radium in drinking water are lime softening, reverse osmosis, and cation exchange. Methods shown to be effective for uranium removal are lime softening at high pH, reverse osmosis, and anion exchange. The two available methods for removing radon from drinking water are granular activated carbon and aeration. For manmade radionuclides, ion exchange can be used.

EPA has developed preliminary cost estimates for technologies that may feasibly remove radionuclides from drinking water. The following estimates are in 1989 dollars. Depending on the amount of water treated, estimated costs range from $0.30 to $0.80 per 1,000 gallons for cation ion exchange; $0.30 to $1.10 per 1,000 gallons for iron and manganese treatment; and $1.60 to $3.20 per 1,000 gallons for reverse osmosis. Preliminary cost estimates for aeration techniques range from $0.10 to $0.75 per 1,000 gallons for systems serving about 100,000 people and 100-500 people, respectively.

Preliminary cost estimates for removing radon from household drinking water systems with point-of-entry treatment devices are a capital cost of $400 to $800 for granular activated carbon and about $900 for aeration, with annual operating costs estimated at $20 per year for activated carbon and $80 per year for aeration.

5.3 Organics Treatment

The organics treatment techniques considered here include granular activated carbon (GAC) and aeration.

5.3.1 Granular Activated Carbon

5.3.1.1 The Treatment Process

GAC works on the principle of adsorption. Adsorption is the transfer of a dissolved contaminant (adsorbate) from a solvent (solution) to the surface of the adsorbent (granular activated carbon). Thus, the contaminant is not changed but instead is held on the surface of the carbon.

The GAC itself is a very porous type of carbon with the property of adsorbing dissolved contaminants onto its surface (see Figure 5-12). Key to its success as an adsorbent is its extremely large internal surface

Figure 5-10. Ion exchange treatment system.

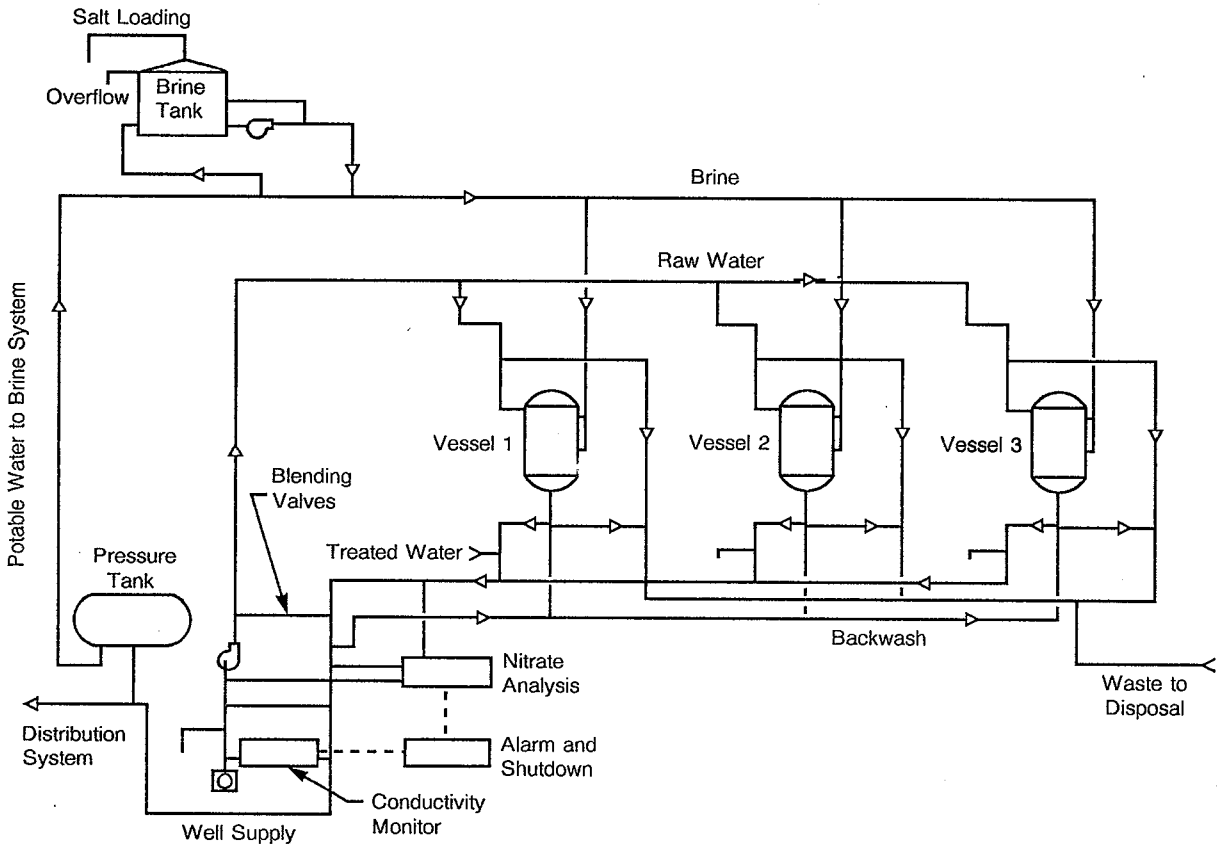


Table 5-5. Removals Possible with Ion Exchange

Cations >90 Percent Removal	Anions >90 Percent Removal
Ba	As (V)
Cd	Cr (VI)
Cr (III)	NO_3
Ag	Se (IV)
	Se (VI)

adsorbed ions like nitrate. Regeneration must be performed frequently, sometimes as often as once per day, creating a potential problem with disposal of the waste regenerant. Ion exchange is not feasible at high total dissolved solid concentrations (> 500-1,000 mg/L) because the ion exchange medium will foul, and the removal process is most effective at lower ionic strengths.

5.2.3.1 Case Study: Ion Exchange

This case study describes the use of ion exchange to remove nitrate from a ground-water supply in McFarland, CA (3). Four wells were affected by nitrate contamination from agricultural runoff (i.e., fertilizers, manure), with raw water levels of 6.8 to 22.1 mg/L as N. Ground water was the sole source of drinking water available.

Ion exchange was chosen because it could be applied at the wellhead with a minimum of operator attention. Plant capacity was 1 MGD. Treatment processes included anion exchange, sodium chloride regeneration with slow rinse and resin declassification, and aerated lagoons and spray irrigation for brine waste treatment. The treated water was blended with raw water at a ratio of 70 percent treated water to 30 percent raw water..An empty bed contact time (EBCT) of 2.5 minutes was used.

The treated water had nitrate levels ranging from 2 to 5 mg/L and the finished (blended) water had nitrate levels ranging from approximately 6 to 8 mg/L. About 2,000 lb of salt were used per day during continuous operation.

5.2.4 Activated Alumina

The activated alumina process is similar to the ion exchange technique described above. Activated alumina is a commercially available product that acts as an ion exchange medium for selected contaminants. This exchange medium is

Figure 5-9. Reverse osmosis treatment system.

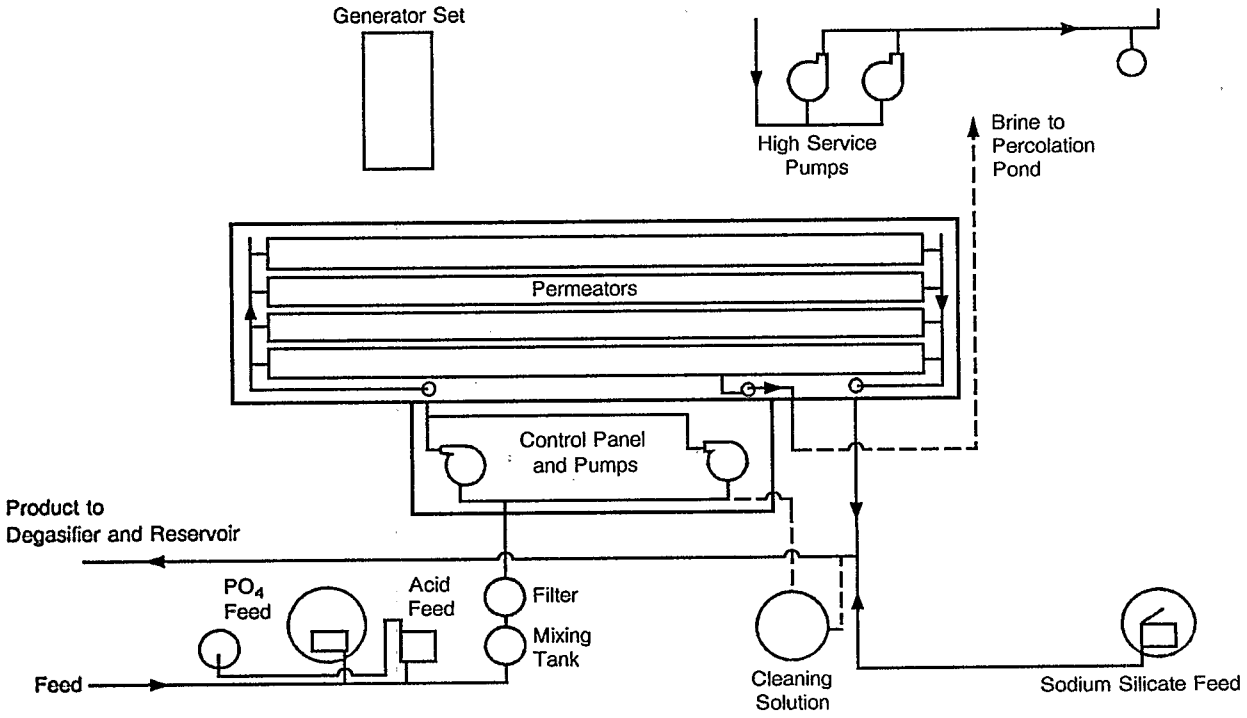


Table 5-4. Removals Possible with Reverse Osmosis

>90 Percent Removal	>70 Percent Removal
As (V)	As (III)
Ba	Hg
Cd	No_3
Cr (III)	
Cr (VI)	
F	
Pb	
Se (IV)	
Se (VI)	
Ag	

Figure 5-10 illustrates an ion exchange treatment system.

Because the ion exchange medium has small internal pore spaces that can become clogged, suspended solids must be removed through prefiltration. Competing ions are also important; as in reverse osmosis, competing ions such as in very hard water can occupy sites on the exchange medium needed for contaminant ions.

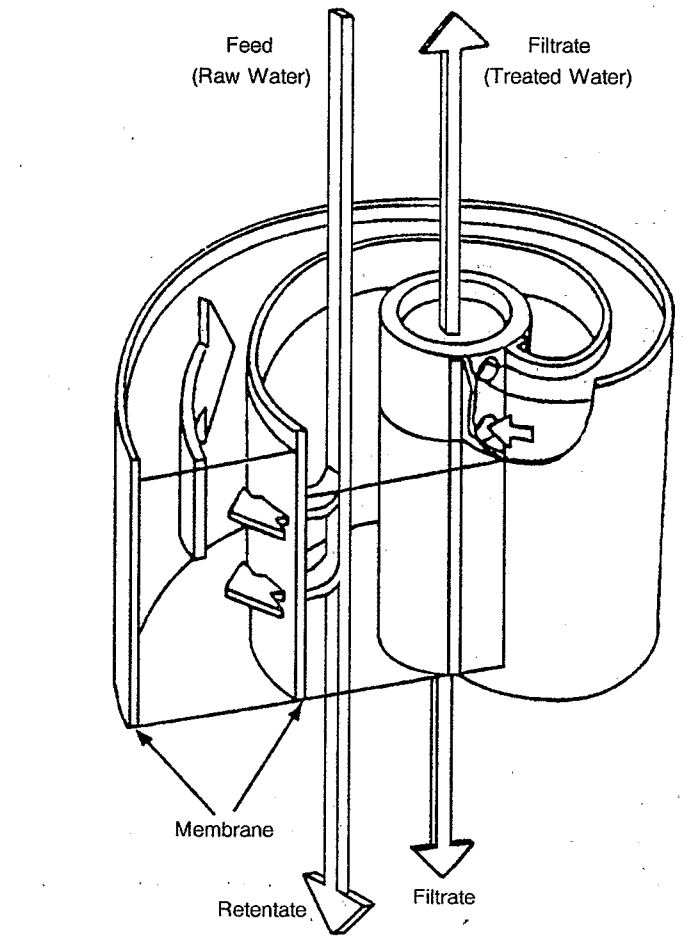
The resin exchange capacity is usually available as a number in milligrams per unit volume of resin. This resin capacity, along with the empty bed contact time, can be used to calculate the resin "break-through" times (i.e., the time when contaminants begin to be detected in the treated water). Table 5-5 summarizes ion exchange's removal percentages for selected anions and cations. The process is effective for barium, radium, and other cations (for cationic resins) and nitrate and selenium (for anionic resins).

While sodium chloride is an inexpensive and convenient presaturant, its use adds sodium to the treated water, possibly making the water unsuitable for those on a salt-restricted diet. In response to this problem, calciform resins (calcium chloride) are currently being developed that do not add sodium to the water.

The advantages of ion exchange are similar to those of reverse osmosis, in that it is also relatively insensitive to flow and thus can be operated on demand. A large variety of resins are available for a variety of applications. For example, resins with higher affinities for specific contaminants (i.e., radium and nitrate) can be purchased. Ion exchange can very effectively remove selected contaminants, with near zero contaminant levels possible in the effluent-treated water.

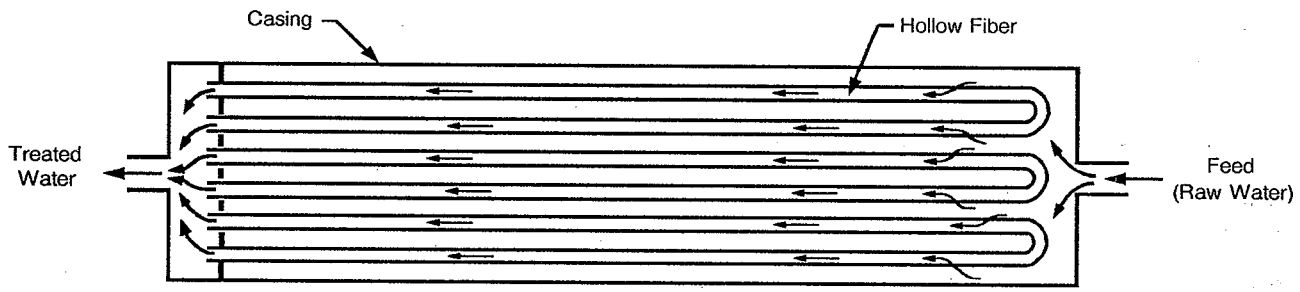
One disadvantage of ion exchange is a phenomenon called effluent peaking: When competition happens among ions, spikes in the contaminant levels occur as the competing ions occupy sites on the exchange medium. Peaking is especially a problem with poorly

Figure 5-8. Two types of reverse osmosis membranes.



Courtesy of Millipore Corporation

Process Flow Through Spiral-Wound Reverse Osmosis Unit



Hollow-Fiber Reverse Osmosis Unit

5.2.3 Ion Exchange

Ion exchange refers to the process of substituting one ion for another on the charged surface of a resin. An exchange medium, often plastic resin, is charged and presaturated most commonly with sodium chloride. When water containing contaminant ions contacts the exchange medium, the contaminant ions, which are preferred by the medium, replace the sodium or chloride, depending on whether cation or anion exchange is desired. After the exchange medium is completely saturated with contaminant ions, the medium must be regenerated with an appropriate brine solution to resaturate it with the desired ion. The resulting waste or regenerant is heavily contaminated and must be disposed of properly.

become concentrated enough that the water left behind can be considered a brine.

Figure 5-8 illustrates two types of reverse osmosis units. In the spiral-wound membrane unit, sheets of membrane material cover each side of a porous water-conducting backing cloth. This arrangement forms an envelope closed on all sides except for one that communicates with a perforated center tube. This membrane, along with a mesh spacer, is wrapped into a tight spiral so that feed water can contact the entire surface of the membrane. Water is pumped into the mesh space outside the membranes under pressure. Since only water can pass through the membranes and collect in the center tube, the water is demineralized and purified.

In the hollow-fiber unit, the semipermeable membrane takes the form of many hair-like hollow tubes. Contaminated water pumped under pressure into the spaces between these tubes allows water to pass into the inside of the tubes, leaving the contaminant behind.

An advantage of the spiral-wound unit is that it is less likely to clog when treating water high in suspended solids. In fact, reverse osmosis usually requires pretreatment (described more fully below). The hollow fiber unit has the advantage of having a much higher membrane area per unit of space occupied by the device. The hollow fiber unit provides about 1,000 ft^2 of membrane per ft^3 of membrane module, while the spiral wound unit provides only 100 ft^2 of membrane per ft^3 of membrane module.

Important process design considerations include the influent suspended solids concentration, the ionic size of the contaminants present, and the membrane type. Membranes are available in specific pore sizes for specific contaminants, and with specific chemical resistances such as to chlorine.

Because the membranes are expensive and subject to fouling, various pretreatment processes are usually necessary. Figure 5-9 shows a reverse osmosis treatment system incorporating pretreatment. Typical pretreatment processes include pH adjustment to protect the membrane, prefiltration to remove particulates capable of fouling the membrane, and sequestration of hardness ions to prevent membrane clogging. (Sequestering agents keep high concentrations of minerals like calcium and magnesium in solution so that they won't precipitate out and clog the membrane)

Table 5-4 summarizes the removal percentages possible for reverse osmosis treatment of inorganic. In addition to inorganic, reverse osmosis also removes trihalomethane precursors (humic and fulvic acids), nitrates, pesticides, and microbiological contaminants (viruses, bacteria, protozoa).

Reverse osmosis might be best suited to waters containing high levels of inorganic chemicals, organic chemicals, and total dissolved solids. Because it is relatively insensitive to total dissolved solids, it has been used successfully in the Gulf Coast area, where total dissolved solids concentrations can be as high as 2,600 mg/L (whereas the ion exchange process, for example, cannot tolerate such concentrations). This process is also relatively insensitive to flow; the device can be turned on and will begin working almost immediately. Reverse osmosis very effectively removes contaminants, with almost zero levels possible in the effluent-treated water. Especially effective removal is possible if a multi-stage system is used in which the water is pumped through additional reverse osmosis units arranged in series.

A major disadvantage of reverse osmosis is its high operating and capital cost; for a small plant (<1 MGD), the operating cost can be a relatively high $3-6 per 1,000 gallons of treated water. Pretreatment (pH adjustment, prefiltration, sequestration of hardness ions) also adds to the cost. In addition to the fouling problems already discussed, membranes can also foul due to biological growths within the unit during periods of disuse, such as during the off-season in a seasonal system like that used for a trailer park. Another significant problem with a reverse osmosis system is that the reject stream can be a high percentage (20-90 percent) of the feed flow. Finally, this reject water or brine, now high in contaminants, must be disposed of properly. When the brine contains high concentrations of radionuclides such as radium-226, disposal can be a problem.

5.2.2.1 Case Study: Reverse Osmosis

This case study describes the use of reverse osmosis to remove radium-226 from several ground-water supplies in Sarasota County, FL (2). The article describes existing facilities rather than newly constructed pilot plants. Raw water radium-226 levels ranged from 3.4 to 20.2 pCi/L. Plant capacities ranged from a low of 800 gpd to a high of 1 MGD. Both hollow-fiber and spiral-wound units were used. Treatment processes included pretreatment (cartridge filtration, pH adjustment, ion sequestration), reverse osmosis, and post-treatment (pH adjustment, degasification, chlorination).

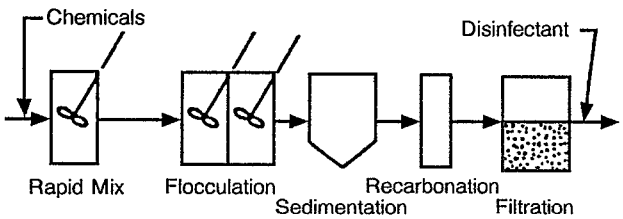
Of eight systems examined in detail, all achieved reductions to levels below the regulatory limit of 5 pCi/L, with product water concentrations ranging from 0.14 to 2.0 pCi/L. Reject water concentrations, however, ranged from 7.8 to 37.8 pCi/L.

Table 5-2. Removal Possible with Conventional Processes

Iron Coagulation	Alum Coagulation
90 Percent Removal	
As (V)	Cr (III)
Cd (pH = 8)	Pb
Cr (III) (pH = 10.5)	
Cr (VI) [using Fe (II)]	
70 Percent Removal	
Ag (pH = 8.0)	Hg
As (V) (pH = 7.5)	Cd (pH = 8.5)

Figure 5-7 shows a treatment system incorporating lime softening. Again, it is in the sedimentation phase that removal of the inorganic contaminants occurs. The recarbonation phase in the illustration involves the addition of CO_2 to the softened water to lower the pH.

Figure 5-7. Lime softening treatment system.



Sometimes, in order to remove both inorganic contaminants (optimal pH of 10-10.5) and hardness (optimal pH of 9-10), a dual-stage process must be used; for example, chemical addition, sedimentation to remove inorganic, recarbonation to lower the pH, and then another sedimentation phase to remove hardness.

Because lime softening to remove inorganic contaminants requires greater addition of lime than is required for softening alone, organic polymers may be used. These polymers are added to increase the rate of settling of the precipitate. Table 5-3 summarizes the effectiveness of softening for the removal of inorganic contaminants. In the table, note that for three important inorganic contaminants (arsenic, barium, chromium), the optimal pH range of > 10 is above the optimal pH range for removal of hardness.

For high volumes of water (>1-5 MGD), the cost of conventional coagulation and lime softening is relatively low. Also, if the water is very hard, lime softening removal percentages will increase because removal depends on enmeshment within the floc particles formed in the softening process. Another advantage is that water utilities have used both of these techniques for many years and are quite familiar with their use.

Table 5-3. Removals Possible with Lime Softening

>90 Percent Removal	>70 Percent Removal
As (V) (pH > 10.8)	As (III) (pH > 10.5)
Ba (pH = 9.5-10.8)	As (V) (pH = 10.0-10.5)
Cd	Cr (III) (pH > 10.5)
Cr (III) (pH > 10.5)	Ag
Pb	

A disadvantage of both techniques is that chemical costs increase when removal of inorganic contaminants is desired. For example, to remove turbidity, alum dosages of 20-40 mg/L are required; to remove arsenic, upwards of 100 mg/L may be required. Thus, chemical costs can be doubled when using these techniques. Also, these techniques create considerably more sludge than normal, which is more difficult to dewater than normal. As mentioned earlier, lime softening may require a two-stage process to optimize removal at different pHs. Finally, these techniques require that chemicals be fed on a relatively continuous basis. Thus, they may be inappropriate for small water supply systems in which the flow of water is often small and intermittent.

5.2.1.1 Case Study: Conventional Treatment

This case study describes the use of conventional treatment for barium contamination in ground-water supplies in northeastern Illinois (1). Small areas had elevated barium concentrations, ranging from 0.4 to 8.5 mg/L. Treatability tests indicated that optimum barium removal could be obtained with 75-175 mg of gypsum (calcium sulfate) per liter of water at a pH of 11.0. The pilot plant had a capacity of 1.5 MGD and incorporated precipitation, direct filtration, and polymer addition.

Barium reduction from 6 mg/L down to 0.5 mg/L was achieved (91 percent removal). Chemical dosages of 100 mg/L gypsum and 0.25 mg/L polymer were used.

5.2.2 Reverse Osmosis

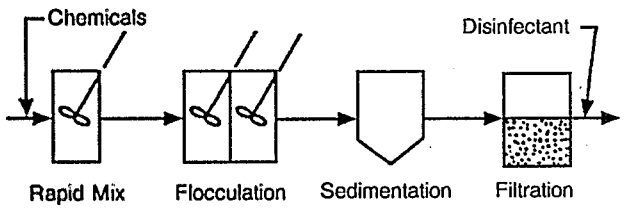
Osmosis is a phenomenon by which solutions of different concentrations are separated by a semi-permeable membrane; water moves from the less to the more concentrated solution. In reverse osmosis, pressure is applied to the more solution and the direction of flow reverses, with the water moving from the more concentrated solution to the less concentrated solution. The semipermeable membrane is permeable to water but not to dissolved ions. Thus, the water passes through the membrane and the contaminants are left behind and eventually

Table 5-1. continued

Contaminant	Treatment Method	Removal Percentage	Relative Treatment Cost* $/1,000 gal 0.3 MGD	1.0 MGD	50 MGD
Mercury					
Inorganic	Lime softening, above pH 10.5	<90	–	0.59	0.41
		>95	1.52	0.59	0.21
	Granular activated carbon		3.18	2.01	1.21
	Reverse osmosis	<85			
Organic	Coag./filt. with powdered activated carbon	50-75	2.19	0.94	0.37 0.21
	Granular activated carbon	>95	1.52	0.59	
Nitrate	Ion exchange (anion resin)	>90	1.11	0.75	0.48
	Reverse osmosis	<90	3.18	2.01	1.21
Nitrite	Breakpoint chlorination	>90	0.05	0.03	0.01
	Ion exchange (anion resin)	>90	1.17	0.85	0.59
	Reverse osmosis	<90	3.18	2.01	1.21
Selenium					
Se IV (Tetravalent)	Ferric sulfate coagulation/ filtration, pH 5.5-7	<80	2.45	0.78	0.22
	Activated alumina	>95	0.78	0.43	0.23
	Reverse osmosis	75-99	3.68	2.28	1.34
	Lime softening	<50	–	0.64	0.41
Se VI (Hexavalent)	Activated alumina	>95	3.91	3.05	2.32
	Reverse osmosis	75-99	3.68	2.28	1.34
Silver					
	Ferric sulfate coagulation/ filtration, pH 7-9	<80	1.40	0.54	0.18
	Alum coagulation filtration, pH 6-8	<80	1.40 –	0.54	0.18
	Lime or excess lime softening	<85	3.18	0.59	0.41
		>90	0.90	2.01	1.21
	Reverse osmosis	<60		0.33	0.11
	Direct filtration				

Source:
Technologies and Costs for the Removal of Inorganic from Potable Water Supplies-Draft Reports. U. S. Environmental Protection Agency, Office of Drinking Water, Washington, DC, 1983-1985.
*Based on constructing new facilities; cost may be lower if existing facilities may be upgraded or optimized.

Figure 5-6. Coagulation/filtration treatment system.



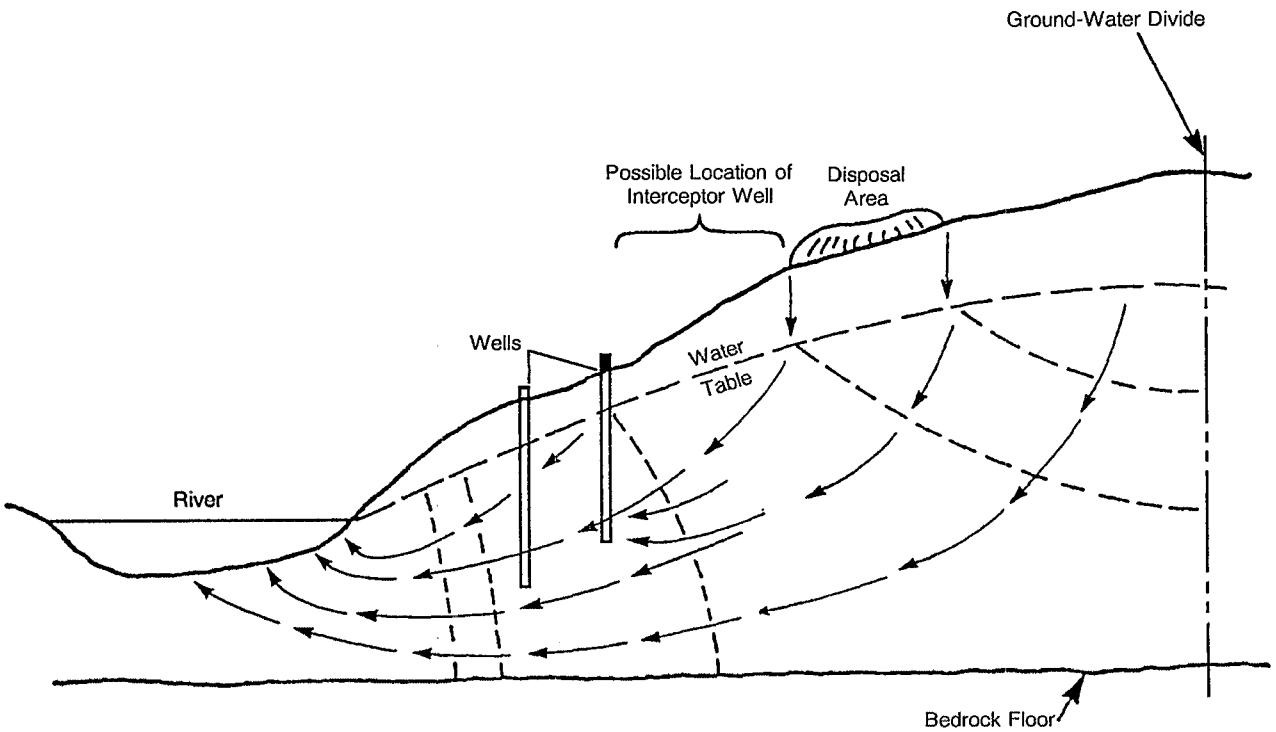
floc particles formed. Iron salts provide a wider range of pH effectiveness than aluminum salts (aluminum sulfate or "alum"). Because coagulation for removal of inorganic contaminants requires higher doses of coagulant than for removal of turbidity alone, coagulant aids such as organic polymers may be used. Table 5-2 summarizes the effectiveness of iron and alum coagulation for removal of inorganic contaminants. Note that coagulation is primarily effective for metals. For nitrate, nitrite, radium, barium, and sulfate, the process is virtually ineffective.

Lime Softening: Water is softened to remove "hardness" from ground and surface water, particularly in the Midwest and Southeast. Hardness is the sum of divalent cations in solution and is due to calcium and, to a lesser extent, magnesium. Hard water contains large amounts of dissolved minerals that cause scaling and excessive soap consumption. In lime softening, lime is added to the hard water, causing the mineral ions and lime to precipitate out. When excess lime softening is used (i.e., higher pH), precipitation of inorganic contaminants can also occur. (If the hardness is noncarbonate hardness, soda ash is used instead of lime.)

Table 5-1. Summary of Treatment Technologies for Inorganic Removal

Contaminant	Treatment Method	Removal Percentage	Relative Treatment Cost* $/1,000 gal		
			0.3 MGD	1.0 MGD	50 MGD
Arsenic					
As V (Arsenate)	Alum coagulation/ filtration, pH 6-7	>90	1.75	0.44	0.19
	Iron coagulation/ filtration, pH 6-8	>90	1.75	0.44	0.19
	Excess lime softening	>90	3.05	0.63	0.40
	Activated alumina pH 5-6	>95	1.22	0.62	0.51
	Ion exchange	<90	0.83	0.51	0.42
	Reverse osmosis	<90	3.32	1.64	1.29
As III (Arsenite)	Oxidation treatment of As III to As V, then above treatment methods				
Asbestos	Conventional filtration	>95	1.41	0.54	0.19
	Direct filtration	>95	1.13	0.40	0.13
	Diatomaceous earth filtration	>95	1.43	0.74	0.35
Barium	Ion exchange	>90	0.80	0.44	0.22
	Lime softening, pH 11	<95	–	0.63	0.41
	Reverse osmosis	>95	3.18	2.01	1.21
Cadmium	Ion exchange	>90	0.80	0.44	0.22
	Excess lime softening	>90	–	0.59	0.41
	Reverse osmosis	>90	3.18	2.01	1.21
	Iron coagulation filtration, above pH 8	<80	1.42	0.54	0.18
Chromium					
Cr III (Trivalent)	Iron coagulation/ filtration, pH 6-9	90-98	1.46	0.55	0.19
	Alum coagulation/ filtration, pH 7-9	90-98	1.46	0.55	0.19
	Excess lime softening Ion exchange	98	–	0.59	0.41
	Ion exchange	<90	0.51	0.29	0.15
	Reverse osmosis	>92	3.18	2.01	1.21
Cr VI (Hexavalent)	Ferrous sulfate coagulation/filtration, pH 7-9.5	>90	1.46	0.55	0.19
	Ion exchange	<90	0.80	0.52	0.32
	Reverse osmosis	>90	3.18	2.01	1.21
Copper	Ion exchange	<95	0.80	0.44	0.22
	Lime softening	>90	–	0.59	0.41
	Reverse osmosis	>95	3.18	2.01	1.21
	Alum coagulation/filtration	>50	1.40	0.54	0.18
Fluoride	Activated alumina, pH 5.5	>90	0.47	0.27	0.14
	Reverse osmosis	>90	2.06	1.21	0.67
	Lime softening	<65	–	0.59	0.41
Lead	Iron coagulation/ filtration, pH 6-9	>95	1.75	0.44	0.19
	Alum coagulation/ filtration pH 6-9	>95	1.75	0.44	0.19
	Lime or excess lime softening	>97	2.98	0.60	0.40
	Ion exchange	<95	0.92	0.36	0.23
	Reverse osmosis	<95	3.32	1.64	1.29
	Direct filtration	<60	1.34	0.33	0.13

Figure 5-5. Interceptor well.



month. However, POU treatment is not recommended for microbiological contamination because of the acute nature of the diseases caused by such contamination. Also, as with bottled water, POU treatment at a single drinking water tap does not minimize inhalation hazards incurred during washing and bathing. EPA does not consider systems using POU to be in compliance with the VOC regulations.

In conclusion, risk reduction requires an understanding of several factors: the overall hydrogeology of the system, treatment level targets in terms of feasibility and cost, and the various control strategies available.

5.2 Inorganics Treatment

Inorganic treatment techniques considered below include conventional treatment (iron and alum coagulation), lime softening, reverse osmosis, ion exchange, and activated alumina. Table 5-1 summarizes treatment technologies for the removal of inorganic chemicals.

5.2.1 Conventional Treatment and Lime Softening

Conventional Treatment: Conventional treatment involves the addition of coagulants, most commonly aluminum or iron salts, to remove color and turbidity from surface waters. This coagulation process also removes inorganic contaminants (if precipitated out of solution) through adsorption and enmeshment in clumps of coagulated sediment referred to as floc particles.

Polyvalent cations and anions such as calcium, magnesium, carbonate, and phosphate can be readily removed by direct precipitation. Direct precipitation is generally accomplished by increasing the pH, as in lime softening, where the pH is increased using lime and sometimes soda ash. Trace anions such as selenium, arsenic, and fluoride are removed by coprecipitation or sorption onto the surfaces of the floc particles formed by iron and aluminum salts.

Figure 5-6 illustrates a typical conventional treatment system that uses coagulation. Removal of the inorganic contaminants occurs through settling in the sedimentation basin after flocculation. A rule of thumb is that coagulation of inorganic chemicals works better with polyvalent cations and anions (charge of ± 2 or greater) than with monovalent cations and anions (charge of ± 1).

The pH of the water is an important process design consideration because it affects the form of the target species (i.e., whether the contaminant is soluble or insoluble), the form of the coagulant, and the type of

Figure 5-3. Drilling a new well.

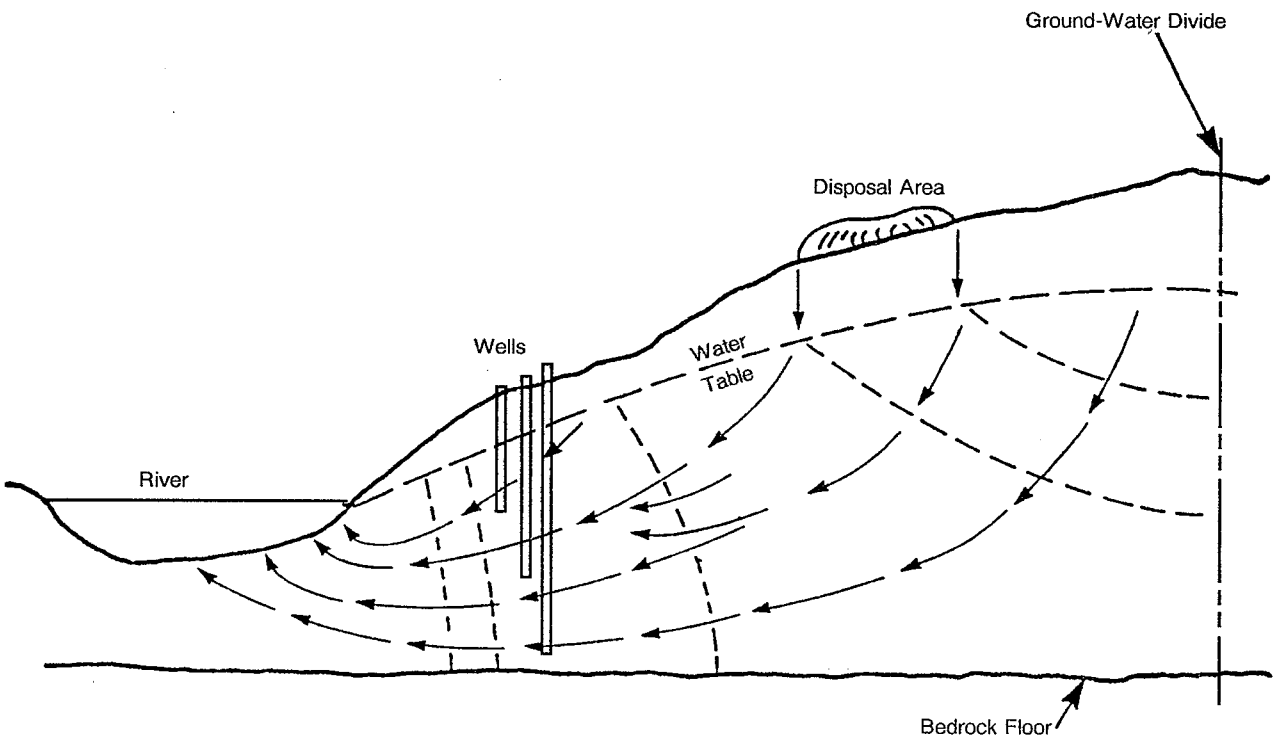
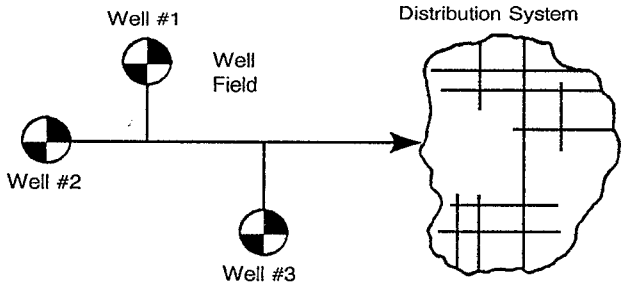


Figure 5-4. Blending existing sources.



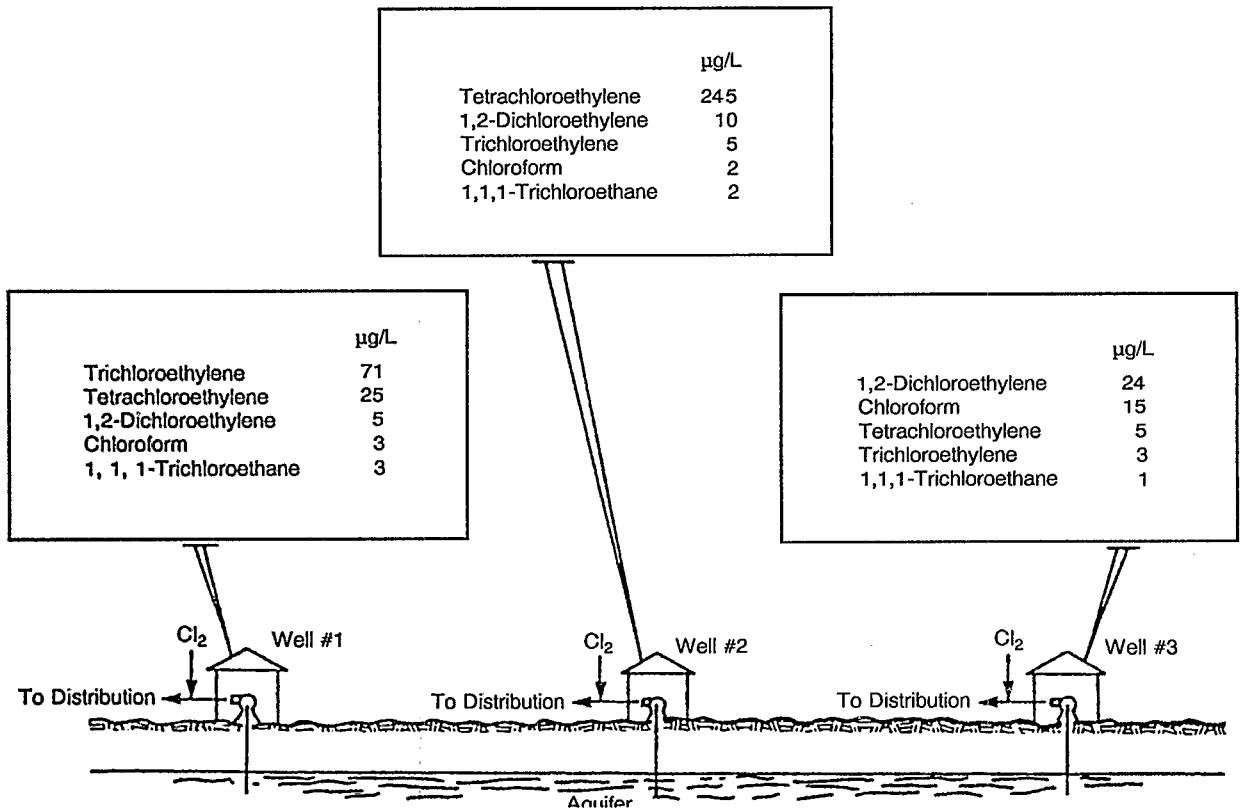
interceptor well is then pumped to waste to remove the contaminant from the aquifer before it can contaminate the drinking water wells. This technique is currently being used in several locations in the U.S. In such locations, without interceptor wells operating, VOC contamination levels were 50-100 µg/L. With the interceptor wells operating, the levels dropped to less than 50 µg/L. The major disadvantage of this approach is that disposal of the wastewater from the interceptor well poses problems. Some recent EPA guidance indicates that the water from the interceptor well may have to be treated to drinking water standards prior to discharge, thus eliminating any cost- savings gained by using this technique.

5.1.3.2 Short-Term Strategies

Short-term strategies include the use of bottled water and point-of-use devices. Two concerns with bottled water are ensuring the quality of the bottled water itself and distributing the water to the customer. Some states certify the quality of bottled water; in areas without state certification, a system for testing and monitoring the bottled water quality may have to be developed. The cost of bottled water can be approximately $50 per household per month. Finally, the use of bottled water does not mitigate inhalation hazards such as from the volatilization of VOCs or radon gas from contaminated water used for washing and bathing.

Point-of-use (POU) devices treat water at a single tap with various existing treatment technologies. Many types are available, based on techniques such as activated alumina, granular activated carbon adsorption, reverse osmosis, and ion exchange. In general, POU devices are suitable for short-term emergencies during which their ability to quickly provide uncontaminated water is an advantage. For example, at a typical Superfund site, it may take six months to install a centralized treatment system at the water supply but only a few weeks to install commercially available POU treatment devices at all of the affected households. Costs for POU treatment range from $20-$60 per household (one tap) per

Figure 5-2. Example of contaminated ground-water supply.



can be easily identified. The tank could be repaired or removed and the contaminated well could be pumped to waste until the contamination concentration dropped to acceptable levels. The first disadvantage of this approach is that identifying sources is often difficult because solvents like trichloroethylene and tetrachloroethylene were used carelessly for many years and dumped in sites such as airports and shopping centers. These chemicals can migrate long distances from the original site to the drinking water supply. Second, even if the source can be identified, pumping to waste might have to continue for years if the contamination is severe and has occurred over several years. Thus, even after eliminating a source, treatment may still be necessary.

Another option is locating a new source of supply—for example, drilling a new well. If the current source is a ground-water supply, it is unlikely that the new source would be a surface water supply because such supplies require state permits and impoundments, and surface water generally requires more involved treatment, such as coagulation or filtration. Figure 5-3 illustrates the potential for contamination of a newly drilled well. If the new well can be drilled beyond the divide shown in the illustration, it will not draw tainted water from the contaminated zone. This option depends on accurately determining the location of the divide and obtaining land beyond it.

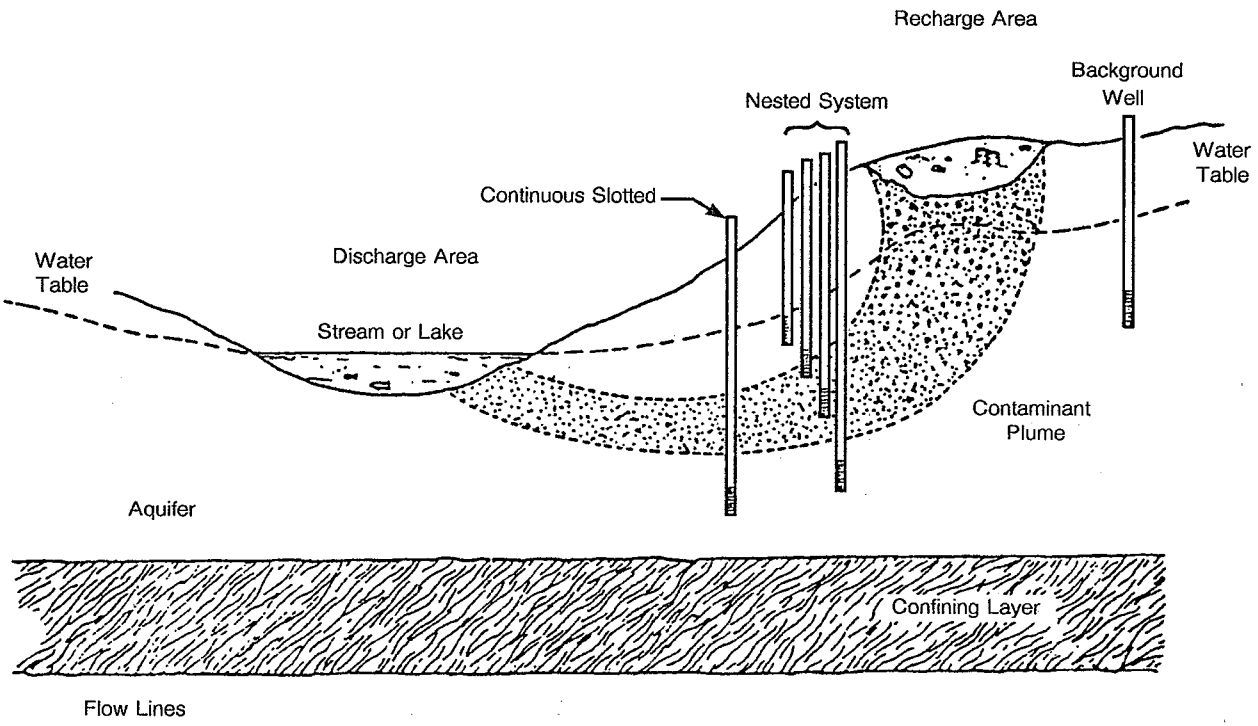
In communities served by groups of wells in wellfields, contaminated water can be blended with uncontaminated water to reduce the concentration of the contaminant through dilution (see Figure 5-4).

The contaminated water can be treated to some extent and then blended, or the contaminated wells can be manifolded together and treated at a central location. On the other hand, individual treatment units like GAC units and aerators can be installed at the wellhouse of each contaminated well. Disadvantages of blending include:

- The ground-water system may not be flexible enough to permit sufficient blending; i.e., the system hydraulics may be such that different wells serve different parts of the distribution system.
- The contaminant concentrations may be too high to achieve an acceptable level via dilution.
- Some states prohibit the use of blending for certain contaminants.
- Consumers may not accept this alternative because it does not involve actual removal of the compound from the water.

Another option is installing an interceptor well (see Figure 5-5). An interceptor well can be drilled upstream of contaminated drinking water wells; this

Figure 5-1. Monitoring wells.



Other data that should be gathered are the type of contaminant, contaminant levels, and the type of water supply. Inorganic contaminants tend to be naturally occurring and show up in ground water in relatively constant levels. In contrast, many organic contaminants enter drinking water supplies as a result of man's activities and thus contaminant levels can vary significantly over time. Other site-specific data to consider include:

- Water quality criteria such as hardness and, for some heavy metals, competing ions for the treatment process.
- Information on contaminant levels, including historical levels, the mix of contaminant, and the relation of these levels to goals for design influent and effluent levels.
- Characteristics of the water supply, including whether it is surface or ground water, the number and location of wells in a ground-water supply, and the supply system configuration (i. e., reservoir, booster pumps).

In fact, the most cost-effective treatment solutions are usually site-specific. For example, existing basins originally designed for storage might be modified to provide aeration for VOC contamination.

5.1.3 Choosing Control Strategies

After initial data gathering, risk managers can examine three types of control strategies : 1) source control, 2) treatment combinations, and 3) short-term strategies. These options could be used to handle a contamination problem in a small supply, such as that illustrated in Figure 5-2. Note the mixture of contaminants; each well contains a number of VOCs at different levels and mixtures with no one contaminant predominating. Also, each well discharges to a different part of the distribution system (a fairly common practice). Thus, treatment would require either manifolding all wells together or installing costly treatment equipment at each well. In the illustration, the only current treatment is chlorination, which would not control the VOC contamination.

5.1.3.1 Source Control

Source control involves the following actions: eliminating a contaminant source, obtaining a new source by drilling a new well, blending contaminated water with uncontaminated water, and operating an interceptor well.

Eliminating a contaminated source is possible if the source, such as a leaking underground storage tank,

Chapter 5

Risk Reduction

This chapter builds on the definition of drinking water problems in previous chapters, by describing the process of rectifying these problems (i.e., "risk reduction"). Section 5.1 provides an overview of risk reduction and control strategies. Section 5.2 highlights inorganic treatment and Section 5.3 outlines organics treatment. Note that risk reduction does not involve further investigation of health risks, but rather is based on the risks defined in EPA Health Advisories and Criteria Documents.

5.1 Overview of Risk Reduction and Control Strategies

5.1.1 General Considerations

Control strategies for drinking water problems must take into account a variety of factors. Among the most important of these is the cost feasibility of various treatment options, especially for small water supplies. Treatment strategies must also account for the ultimate fate of the contaminant in the environment. For instance, the degradation product of some contaminants in the environment can be more toxic than the original contaminant. The chemicals dichloroethylene, trichloroethylene, and tetrachloroethylene, for example, break down into the gas vinyl chloride in ground water.

Another factor is scientists' ability to test the extent of ground-water contamination, especially for contaminants that exert their health effects at very low levels. To determine compliance, EPA must be reasonably confident that the reported value for a ground-water sample is close to the true value. To this end, EPA has established two measurement parameters, the minimum detection limit (MDL) and the practical quantification level (PQL). The MDL is the minimum concentration of a substance that can be measured and reported with 99 percent confidence that the true value is greater than zero. These MDLs, however, are measured by sophisticated labs under nonroutine conditions; moreover, MDLs indicate the presence of a chemical (i.e., detection) not measurement. Therefore, the PQL is generally 5 to 10 times the MDL, so that a sufficient number of laboratories can report results within a reasonable range of the true value (generally $\pm$ 40 percent at low levels, $\pm$ 20 percent at higher levels). Any treatment concentration goal must be determined in terms of the ability to analytically determine contaminant concentrations after treatment.

5.1.2 Taking the Initial Steps In Planning a Risk Reduction Strategy

When a drinking water contamination problem is identified, several important initial steps should be taken. A reliable data base must be developed, through routine monitoring of existing nearby wells (private, industrial, USGS, and state geological survey wells); drilling of additional monitoring wells; and assessment of existing hydrogeological data. Figure 5-1 illustrates a contaminated site with various monitoring wells. Note that the background well does not show the contamination and that the nested well system reveals the extent of contamination. The continuous slotted well is also designed to determine the vertical extent of contamination; but, because water enters along most of its length, it detects the presence of contaminants but not their depth.

In some cases, especially for ground water, these data can be plugged into mathematical models to determine the location of the source of contamination and to project future conditions (e. g., the impact of continued pumping or cessation of pumping).

Table 4-2. Health Effects of Some Chlorinated Halogenated Hydrocarbons

	CNS Depression	Sensitization of Heart	Liver Injury	Kidney Injury	Cancer
Methanes					
Carbon tetrachloride	+	+	+ + + +	+ +	+
Chloroform	+	+	+ + +	+ + +	+
Dichloromethane (methylene chloride)	+	-	+ -	-	+
Ethanes					
1,1-Dichloroethane	+	+	+		
1,2-Dichloroethane	+		+	-	+
1,1,1-Trichloroethane	+	+	+ -	-	-
1,1,2-Trichloroethane	+		+ +	-	+
1,1,2,2-Tetrachloroethane	+		+ +	+ +	
Hexachloroethane	+			+	+
Ethylenes				+	+
Chloroethylene (vinyl chloride)	+		+ +	-	+ + +
1,1-Dichloroethylene (vinylidine chloride)	+		+ + +	-	+
1.2-Trans-dichloroethylene	+		+ +		
Trichloroethylene	+	+	+	+ -	+
Tetrachloroethylene (perchloroethylene)	+	-	+ -	+ -	+

4.3 References

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2. *Federal Register* 50(219): 46980, 1985.

3. Klaassen, C.D., M.O. Amdur, and J. Doull, eds. Casarett and Doull's Toxicology, 3rd Edition. Macmillan, New York, NY, 1986, pp. 846-848.

4. Drinking Water and Health. National Academy of Sciences, Washington, DC, 1977, pp. 169.

5. Klaassen, C.D., M.O. Amdur, and J. Doull, eds. pp. 840-841.

4.2.2.4 *Fungicides*

Fungicides are used to control fungus diseases on plants, seeds, and produce. The fungicides include organomercurial compounds, dithiocarbamates, hexachlorobenzene, and pentachlorophenol. These chemicals are less of a chronic, long-term threat to drinking water than those discussed previously, but they can have toxic and even carcinogenic effects in doses of sufficient duration and amount. Pentachlorophenol is of concern because commercial samples have been shown to be contaminated with highly toxic dibenzodioxins and dibenzofurans.

4.2.3 Solvents and Vapors (Volatile Organic Compounds)

This class of contaminants includes halogenated hydrocarbons and aromatic hydrocarbon solvents. Many of these chemicals, especially chlorinated solvents like trichloroethylene (TCE) and perchloroethylene (PCE), have contaminated drinking water sources; for example, by leaching from hazardous waste sites or as a result of TCE being used in the past for cleaning septic tanks.

4.2.3.1 *Halogenated Hydrocarbons*

These chemicals are widely used because they are effective yet relatively inflammable solvents, as opposed to kerosene or gasoline. Also, halogenated hydrocarbons are formed during the chlorination of drinking water when chlorine combines with organic material in the water.

The halogenated hydrocarbons tend to have similar health effects; hence, carbon tetrachloride will be used as an example. Carbon tetrachloride in high doses causes CNS depression and, as a result, was once used as an anesthetic. It can also sensitize the heart muscle to catecholamines (hormones such as epinephrine) and thus can cause heart attacks. It can cause kidney injury, liver injury, and cancer in laboratory animals (Class B2). As mentioned earlier, high blood alcohol levels can act as a potentiator for carbon tetrachloride's damaging effects on internal organs.

Table 4-2 summarizes the health effects of other halogenated hydrocarbons. Plus signs (+) indicate a harmful effect, minus signs (-) indicate a lack of effect, and both a plus and a minus indicates a less significant effect. Among the methanes, chloroform is a trihalomethane formed during drinking water chlorination. Chloroethylene (vinyl chloride) receives three plus signs under cancer because it has been established as a human carcinogen, while the others have been established as probable human carcinogens based on results of animal studies. Also noteworthy are trichloroethylene and tetrachloroethylene (perchloroethylene). These chemicals are very common contaminants of drinking water; although they are listed as probable carcinogens, they cause cancer in laboratory animals only at very high doses. Also, researchers have observed that when perchloroethylene and tetrachloroethylene degrade naturally in ground water, vinyl chloride has been formed as a degradation product.

4.2.3.2 *Aromatic Hydrocarbon Solvents*

The aromatic hydrocarbon solvents include benzene and toluene. Benzene enters drinking water supplies as a component of gasoline, which most often contaminates water supplies by leaking out of corroded underground storage tanks used by gas stations. Acute doses of benzene cause CNS depression, but chronic doses are more important with regard to drinking water. Chronic exposure to benzene in drinking water can cause bone marrow depression - an impairment of the bone marrow's ability to produce blood cells. More importantly, chronic benzene exposure can cause leukemia in humans and has been classified as a human carcinogen by EPA (Class A). In comparison to benzene, toluene is a relatively safe solvent (Class D). However, in acute doses it can also cause CNS depression, liver dysfunction, and kidney dysfunction, and has been associated with female reproductive effects (4).

4.2.4 Other Important Synthetic Organic Chemicals

Polychlorinated biphenyls (PCBs) are synthetic compounds that were manufactured in great quantities from 1929 until the late 1970s, largely for use in electrical equipment as nonconductive heat transfer fluids. PCBs are lipid soluble and thus biomagnify in the food chain and are teratogenic and carcinogenic in laboratory animals. PCBs first gained notoriety after an incident in Yusho, Japan in 1968 in which about 1,300 people used rice oil for cooking that had been heavily contaminated with PCBs. These people suffered a variety of health effects, including skin irritation, eye discharges, GI tract disturbances, and reproductive and nervous system disorders. Clearly, this incident was a highly acute exposure to PCBs; the effects of long-term, low-level exposure to PCBs, such as would be found in drinking water, have not yet been fully determined (5).

Fortunately, both lab tests and antidotes are available for acute poisoning with organophosphorus pesticides. Although currently available organophosphorus insecticides do not cause delayed neurotoxicity, some of the previously available pesticides did cause delayed neurological problems such as weakness, lack of muscle coordination, and sensory disturbances.

Carbamates: The carbamate insecticides, such as carbaryl and aldicarb, have toxicities very similar to the organophosphorus insecticides. Like the organophosphorus pesticides, these widely used chemicals also act by inhibiting cholinesterase. The toxic effects of carbamates may be more easily reversed than those of the organophosphorus pesticides. Current evidence does not seem to suggest carcinogenicity as a toxic effect of the carbamates. Aldicarb used on potato crops in Long Island, NY, has contaminated ground-water aquifers.

Botanical Insecticides: The botanical insecticides are derived from various plants and include the compounds nicotine, pyrethrum, and rotenone. Insecticides used in the home usually contain pyrethrum and generally have a low order of human toxicity. Insecticides containing nicotine are considered the most toxic of the botanicals.

4.2.2.2 Fumigants

Fumigants are pesticides in gaseous form that can be used to treat difficult-to-reach areas such as insects in grain stored in grain elevators and insects in the soil.

Fumigants include cyanide compounds, methylbromide, dibromochloropropane (DBCP), and ethylene dibromide (EDB). Acute doses of methylbromide cause CNS depression and pulmonary edema; in California there have been more deaths due to acute poisoning with methylbromide than the highly toxic organophosphorus pesticides. However, it is not as much of a problem in drinking water as DBCP and EDB.

DBCP has been used extensively in California for soil fumigation and has contaminated several drinking water sources. In Nebraska, it has migrated from treated grain into drinking water supplies. EDB has contaminated drinking water sources in Florida, Georgia, Connecticut, Massachusetts, Hawaii, and other states. Both EDB and DBCP depress the CNS and cause pulmonary edema in acute doses, and have been shown to be potent carcinogens in laboratory animals. DBCP has also been associated with testicular injury and sterility in workers using and manufacturing it. As a result of their probable human carcinogenicity and reproductive effects, many uses of EDB and DBCP have been banned.

4.2.2.3 Herbicides

Herbicides, chemicals used to kill plants, are used in greater quantities than insecticides in the U.S. Herbicides are added directly to the soil and thus readily enter the ground water.

Chlorophenoxy Compounds: The chlorophenoxy compounds include 2,4-D, 2,4,5-T, and 2,4,5-TP (silvex). These compounds can have toxic effects on the liver, kidney, and CNS, but clinical reports of poisoning are rare. The compounds are rapidly excreted into the urine, with a half-life of 24 hours in humans. The most well-known and controversial of the chlorophenoxy compounds is 2,4,5-T, which was combined with 2,4-D to create the defoliant Agent Orange used in the Vietnam War. When 2,4,5-T and 2,4,5-TP are manufactured, a contaminant called tetrachlorodioxin (TCDD, or dioxin for short) is inadvertently produced. Dioxin can also be produced during the combustion of certain substances. This chemical is the most toxic manufactured chemical known. In sufficient doses, dioxin is a potent teratogen and carcinogen in laboratory animals (Class B2), and causes liver injury and general tissue wasting. At lower doses, it causes a form of acne called chloracne, which concentrates between the eyes and hairline.

Clinical reports of acute dioxin poisoning are rare, and in humans chloracne seems to be the worst effect seen so far. Dramatic interspecies differences exist for the effects of dioxin; the LD_{50} for guinea pigs is about 1/10,000 of the LD_{50} for hamsters. Fortunately, evidence collected so far indicates that man's reaction to dioxin resembles that of the hamster more than that of the guinea pig. However, dioxin contamination must be considered a serious environmental problem. In Times Beach, Missouri, dioxin contamination forced the abandonment of 800 homes in 1984.

Other Herbicides: Other herbicides include dipyridyl compounds, triazines, and amides. Paraquat is an example of a dipyridyl compound that can cause severe lung injury through inhalation or GI tract absorption. The triazines include the compound atrazine, which seems to have a low order of toxicity. However, because this abundantly used herbicide has been detected in drinking water with increasing frequency, further study is required. Structurally similar to the triazines is the herbicide amitrole (aminotriazole), which attacks the thyroid and causes cancer in laboratory animals.

Among the amides is the chemical alachlor, which is used extensively in the U.S., especially on corn. Other examples of amides are propachlor and propanil. Although the amides have a low acute toxicity, they have caused severe skin irritation, and have been established as carcinogenic to rats in recent studies.

although there is no epidemiological evidence to support this conclusion, ingested uranium deposits in the bone in the same manner as radium. Through chemotoxic effects, uranium can damage the kidneys. A study of uranium occurrence in the late 1970s conducted by the U.S. Geological Survey provides the basis for an estimate of the actual natural uranium concentra-tions in public water systems. Analysis of the data from this study indicates that approximately 20,000 public water supplies (both surface- and ground-water) have elevated natural uranium concentrations; the average was approximately 2 pCi/L. Research is ongoing to determine the excess health risk due to this level of contamination.

The isotope radon-222 is the subject of great public concern lately. Inhalation of the short-lived progeny of radon-222 can cause lung cancer; less is known about the risks of ingested radon. Although most of the total amount of radon-222 that enters homes comes through the soil, it can also enter homes by degassing from a dissolved state in drinking and washing water. This degassing occurs when water is heated and/or aerated, such as during clothes and dish washing and showering and bathing. If the concentration of radon-222 in the water is high enough, using it can bring indoor radon levels above the EPA guideline of 4 pCi per liter of indoor air.

4.2.2 Pesticides

Pesticides encompass a wide variety of compounds formulated specifically to destroy plant or animal life including insecticides, rodenticides, fungicides, herbicides, and fumigants. Pesticides are used widely in the U.S. and often eventually contaminate drinking water. EPA has banned many of the uses of some of these pesticides.

4.2.2.1 Insecticides

Insecticides can be divided into organochlorine, organophosphorus, carbamate, and botanical insecticides. Within each group, the pesticides have similar characteristics; risk assessors use such categories to make sense of the bewildering array of commercially available insecticides.

Organochlorine Insecticides: This category was commonly used in agriculture in the past and includes the chlorinated ethanes, chlorinated cyclodienes, and other chlorinated compounds.

DDT is the most well-known of the chlorinated insecticides and was used extensively from World War II until 1972, when it was banned in the U.S. It is a highly lipid-soluble compound and thus is stored in fat. In fact, most Americans have DDT concentrations in their fat of 5-7 ppm. DDT is biomagnified in the food chain; i.e., smaller organisms absorb the compound and then are eaten by progressively larger organisms, until DDT attains a relatively high concentration in organisms such as fish, which are then eaten by animals and people.

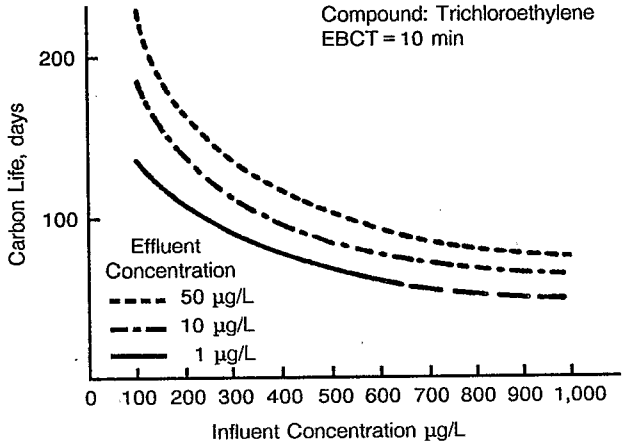
DDT is not particularly toxic to humans and most other higher animal life, except in extremely high doses. As a result, it was applied in much greater quantities than were necessary. Then effects started to be noticed. For example, DDT caused certain bird species (for example, the Peregrine falcon) to produce overly fragile egg shells that broke before hatching. The toxicology of DDT stems from its ability to increase production of P-450 enzymes. These enzymes (see Section 4.1.4) metabolize foreign compounds within the body. Apparently, they can also metabolize endogenous compounds like estrogens, which can interfere with proper egg shell growth. In addition, recent experiments with laboratory animals exposed to DDT have shown an increased incidence of liver tumors. However, whether this observation can be extrapolated to humans remains to be answered. Methoxychlor is a compound similar to DDT, but it is not as persistent in the environment.

An important subgroup of organochlorines are the chlorinated cyclodienes. These chemicals include aldrin, dieldrin, endrin, heptachlor, and chlordane. These pesticides are similar to DDT but are more toxic and have caused many human fatalities. Like DDT, they are lipid soluble and stored in fat, and thus are biomagnified in the environment. They have also caused cancer in laboratory animals. Thus, their registration for use on agricultural crops was suspended in the mid-1970s.

Also similar are other chlorinated hydrocarbons such as lindane, toxaphene, mirex, and kepone. In general, the organochlorine insecticides cause some CNS stimulation, induce P-450 production, increase cancer incidence in laboratory animals (lindane, less so), and persist in the environment to some degree.

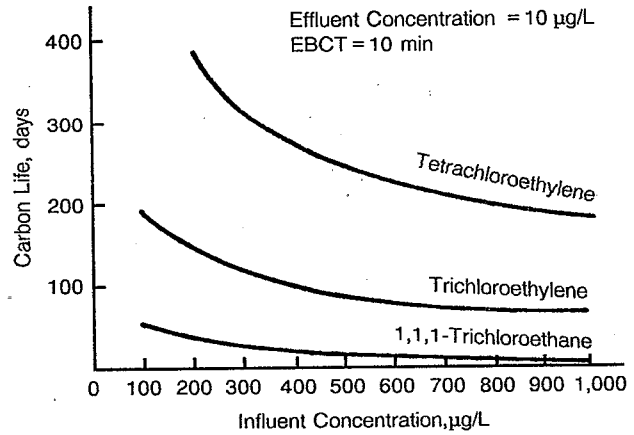
Organophosphorus Insecticides: These insecticides have largely replaced the chlorinated hydrocarbon insecticides because they do not persist in the environment and have an extremely low potential to produce cancer. However, they have a much higher acute toxicity in humans than the organochlorines. A typical example of an organophosphorus insecticide is parathion, which must be metabolized to the compound paraxon to exert its toxic effect. This toxic effect stems from the compound's ability to inhibit the enzyme cholinesterase, a crucial chemical for the regulation of the nerve transmitter acetylcholine. Thus, acute effects of poisoning with organophosphorus insecticides include fibrillation of muscles, low heart rate, paralysis of respiratory muscles, confusion, convulsions, and eventually death. (Another organophosphorus pesticide called malathion is less toxic in acute doses than parathion.)

Figure 5-14. Effect of contaminant concentration on carbon life.



1,1,1- trichloroethane, about 5 months for trichloroethylene, and about 1 year for tetrachloroethylene. Thus, when costing out a GAC system, plant managers must consider the level and type of contaminant.

Figure 5-15. Effect of compound on carbon life.



5.3.1.3 *Facility Design Considerations*

The three major components of a GAC system are the carbon contactors themselves; the transfer system for moving carbon from the contractors to either on- or off-site regeneration; and the regeneration system. Figure 5-16 shows a schematic of a GAC treatment system. Carbon contactors can be operated in either an upflow or downflow mode. In general, upflow contactors are used when a very long contact time, perhaps 1 to 2 hours, is needed and suspended solids must be removed in addition to organics. A disadvantage of upflow operation is some carryover of fine carbon particles ("fines"). Downflow contractors are used where contact times can be expected to be 30 minutes or less.

Contractors can also be either pressure or gravity units. Pressure units allow pumping directly from the well, through the contactor, and into the distribution system. Generally, the contractors cause a 10 psi pressure drop, and usually the existing well pump can still be used. In some cases, a clear well (storage tank) and booster pumps may have to be used. Gravity contractors are generally used for surface water treatment plants of 10 MGD or greater. Such large plants would have to install too many pressure contractors, which can only be made so large, to handle the large water flows. Gravity contractors can also be created by modifying existing gravity-fed sand filters or by installing new concrete contractors.

Multiple contractors can be arranged in either parallel or series operation. Series operation has the advantage of better utilization of the carbon because the first contactor in the series can be allowed to become completely exhausted before regeneration or replacement. In contrast, with parallel operation, as soon as breakthrough occurs in any one contactor, that contactor must be regenerated or replaced before the effluent level rises above an acceptable level. In one study of a GAC system in Long Island, NY that was treating aldicarb and carbofuran contamination, the use of series operation cut carbon usage rates — and thus costs — by one-half (8). However, such savings may not be possible with all compounds.

The carbon transfer system must be designed to minimize carbon loss due to abrasion. The hydraulics of the carbon slurry system, the velocities within the system, and the materials of construction all affect carbon loss.

The regeneration system drives organics off the saturated GAC by heating it in a multiple-hearth or fluidized-bed furnace. Table 5- 9 provides general guidelines for choosing a regeneration option.

Off-site disposal can be a problem if the saturated carbon is classified as a hazardous waste. Off-site regeneration is usually performed by companies that regularly pick up saturated carbon and replace it with regenerated carbon. On-site regeneration usually requires a carefully designed system that includes dewatering of the carbon before regeneration so that energy will not be wasted heating wet carbon. If sufficiently large amounts of carbon are regenerated, the system must be designed such that the off-gases from heating the organic-rich carbon do not contaminate the environment. In one system, regeneration of large amounts of carbon that had treated prechlorinated water resulted in dioxin emissions. Changing to post-chlorination reduced the emissions to acceptable levels (9).

Figure 5-16. GAC treatment system.

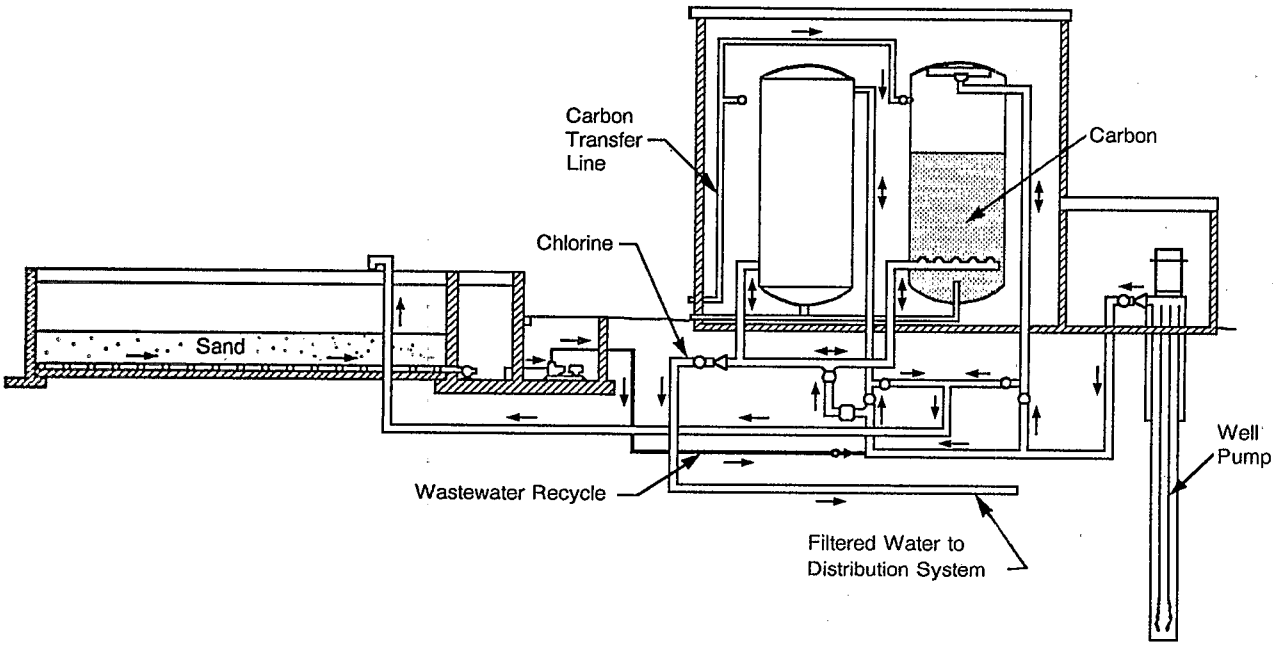
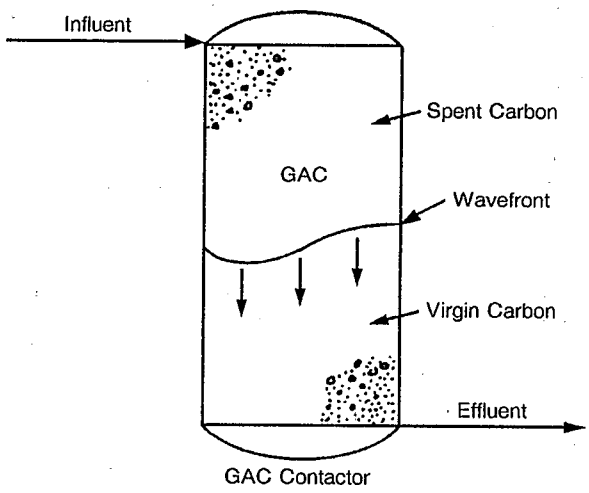


Table 5-9. Regeneration Options

Option	Carbon Exhaustion Rate, lb/day
Off-site disposal	<500
Off-site regeneration	500-2,000
On-site regeneration	>2,000

Figure 5-17. Wavefront within GAC contactor



5.3.1.4 *Operational Issues*

An operational problem called desorption can occur when contaminant influent levels drop; since the GAC process is an equilibrium phenomenon, a drop in the influent concentration can actually cause sloughing off of organics from the carbon.

Another problem is replacement, which occurs when one contaminant is more preferred by the GAC; the more preferred contaminant can replace the less preferred contaminant that has already adsorbed onto the surface of the carbon.

Bacteria can grow on the carbon. The types of bacteria, and the health effects of this growth within the context of the entire treatment system, require further study.

Another important operational issue is "mass transfer," or how the zone of spent GAC moves within the contactor vessel. If the zone proceeds with an even wavefront (see Figure 5-17), the carbon is used efficiently. If the wavefront is upset (i.e., mixing of virgin with spent carbon), premature breakthrough can result. Changing influent concentrations, changing organic compounds, and the manner of backwashing can all affect the movement of the spent zone.

Finally, waste disposal is an important issue. In addition to disposal of spent carbon (for those systems not regenerating), the contractors must be backwashed both initially to remove fines and, with some ground waters, periodically to remove solids. This backwash must be either treated or disposed of properly.

5.3.1.5 Cost

The capital costs of a GAC system always include three major components: contractors, the GAC itself, and piping. Many other site- specific costs can be added to these major components, including:

- Raw water holding tank
- Restaged well pump due to excessive pressure drop through contractors
- Contactor building (needed in cold climates to prevent freezing)
- Chemical feeding equipment
- Clear well (storage tank) and pumps
- Backwash storage tank

Figure 5-18 shows the relationship between system size and capital cost based on the results of a survey of GAC system capital costs in the U.S. (4). In general, costs rise linearly with system size; the outliers represent systems that incurred the additional costs described above. Thus, if the EBCT—the main determinant of system size—can be estimated, the expected total capital cost can also be estimated. Estimation of operating and maintenance (O&M) costs is not as easy. Figure 5-19 illustrates the relationship between system size and O&M cost. Note that no clear relationship emerges. Different areas throughout the U.S. have different contaminants and contaminant levels that produce different carbon usage rates—the main determinant of O & M cost

5.3.1.6 Case Study: Granular Activated Carbon

This case study describes the use of GAC to treat VOC contamination of ground water in Washington, NJ (10). The contaminated supply was a single well with a capacity of 550 gpm (0.792 MGD). The well was contaminated with PCE at 50-500 µg/L, TCE at 1-10 µg/L, 1,1,1- trichloroethane at 1-20 µg/L, and carbon tetrachloride at 1-5 µg/L. The well was operated about 9 hours each day; the contaminant levels varied throughout the day..

A GAC system was installed that incorporated two downflow, pressure contractors operating in parallel. Due to high solids concentrations in the raw water, backwashing was performed about once a month. The washwater was sand-filtered and recycled. An EBCT of 10.5 minutes was used. When the water was treated to below the regulatory limit for PCE, the carbon usage rate was about 100 lb of GAC per million gallons of water treated.

5.3.2 Aeration

5.3.2.1 The Process

The aeration or "air stripping" process mixes contaminated water with air so that the contaminants can volatilize and escape into the atmosphere. (This air stream is sometimes also

Figure 5-18. Capital costs for GAC systems.

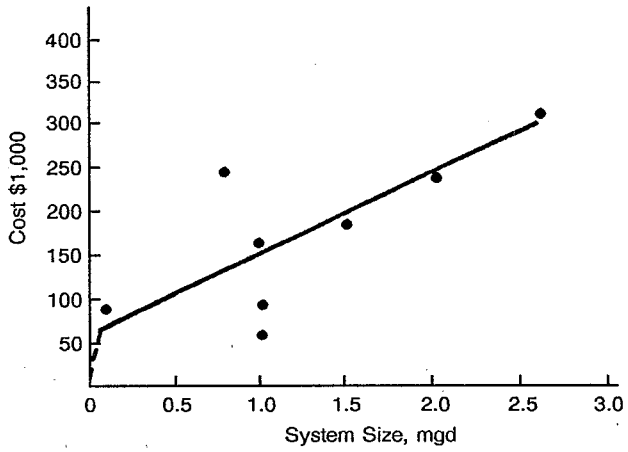
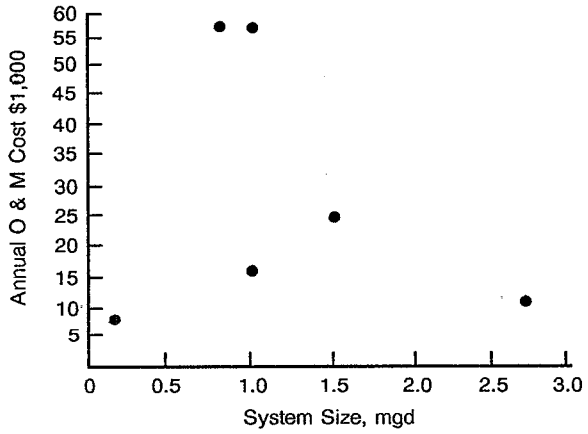


Figure 5-19. Annual O & M costs for GAC systems.



treated.) The more volatile a compound is, the easier it is to remove it from water through aeration.

Treatment system designers use a constant called Henry's Law to compare the volatility of compounds. Table 5-10 gives Henry's Law constants for several contaminants. The VOCs have relatively low solubilities, high vapor pressures, and relatively high Henry's Law constants. Note that vinyl chloride has a very high Henry's Law constant. As a result, EPA has designated the packed tower aeration (PTA) process as best available technology for vinyl chloride; whereas for other regulated VOCs, EPA has designated both GAC and PTA as best available technology. Also, vinyl chloride is very poorly adsorbed onto GAC.

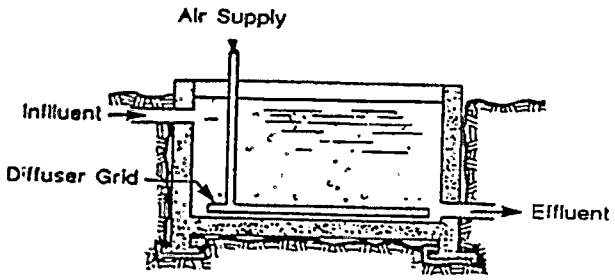
5.3.2.2 Equipment

The two main types of aeration equipment are diffused air units and waterfall units. Diffused air units inject air into a water basin (see Figure 5-20);

Table 5-10. Henry's Law Constants for Organic Chemicals

Type of Organic Chemical	Henry's Law Constant, Dimensionless Units
VOCs	
Vinyl chloride	285
TCE	0.44
PCE	0.88
Cis-1,2-dichloroethylene	0.18
Posticides	
Aldicarb	1×10^{-7}
Chlordane	0.015
DBCP	0.011
Chlorinated aromatics	
PCB	0.021
Dichlorobenzene	0.086

Figure 5-20. Diffused air basin.



in the design shown, air enters the basin at the bottom and disperses into many smaller bubbles as it passes through the diffuser grid and rises to the surface.

Waterfall units allow water to fall through air. The most appropriate waterfall type of unit for the removal of VOCs is the PTA system (see Figure 5-21). In this system, contaminated water flows down through a column containing specially shaped packing material that is designed to disperse the water into many small droplets. A blower forces air from the bottom of the column toward openings at the top. When this air contacts the dispersed water in the packing, contaminants leave the water and enter the moving air stream. This air stream can then be treated to prevent atmospheric pollution.

Other less complicated waterfall types of units have been used, including open cascade systems that simply direct a stream of turbulent water over a spillway, spray aeration units that direct water through many nozzles over an open basin, and multiple or slat tray units that use slats instead of packing material.

Two recent waterfall designs are the catenary grid unit and the Higee system. In the catenary grid design (see Figure 5-22), water falls through a series of parabolic wire grids mounted within a cylindrical column; the grids serve the same purpose as the packing in PTA systems except that the grids "fluidize" the falling water between them, momentarily slowing the water's passage through the column. The efficiency of a catenary grid system is a function of the number of grids used. Although the catenary grid design allows a lower column than with standard packing materials, much higher air flows, and thus energy costs, are required.

In the Higee system (see Figure 5-23), water is pumped into the center of a spinning disc of packing material. Centrifugal force moves the water outward while air is pumped in a countercurrent flow toward the center of the unit. Existing Higee units are best suited to temporary short-term treatment(less than 1 year) at flows less than about 100 gpm. However, future designs may be able to handle higher flows at permanent systems.

5.3.2.3 Process Design Considerations

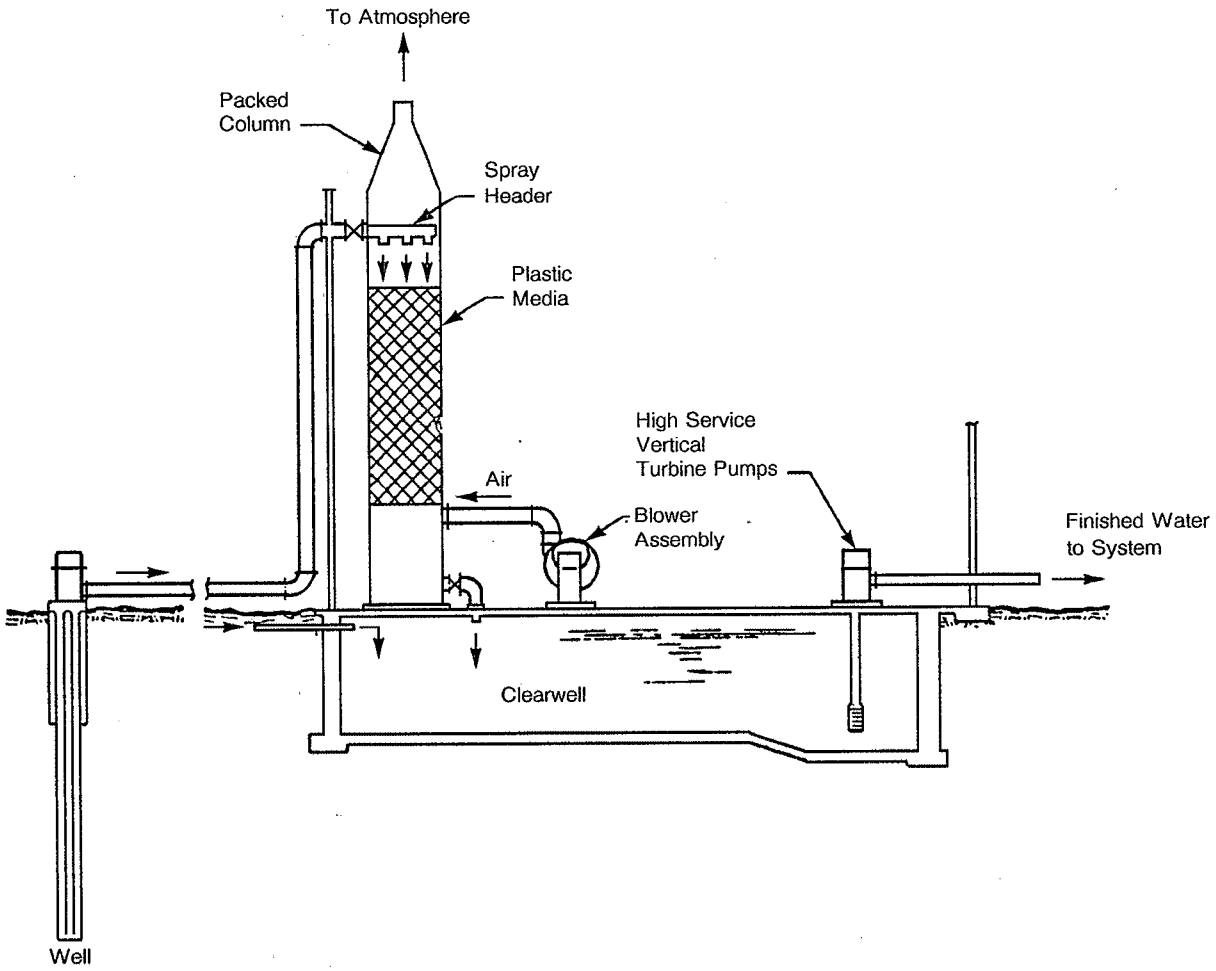
The diffused air system can be improved by increasing basin depth, producing smaller bubbles, optimizing basin geometry, and increasing gas flow.

Process design considerations for PTA must take into account the following considerations:

- Type of compound
- Concentrations (µg/L)
- Type of packing material
- Air/water ratio (ft^3/ft^3)
- Liquid loading rate (gpm/ft^2)
- Packing height (ft)
- Water temperature

Figure 5-24 illustrates the effect of the type of compound on two important variables, packing depth and air/water ratio. Note the marked differences in the design variables for the three contaminants shown. Figure 5-25 shows the relationship between packing height, water temperature, and removal efficiency. The higher the water temperature, the lower the packing height required for high removal efficiency. Heating the raw water is usually not cost-effective for typical drinking water system flowrates. However, in temporary treatment situations and low flowrates, water has been heated to increase tower efficiency.

Figure 5-21. Packed tower aeration system.



5.3.2.4 *Facility Design Considerations for PTA*

Several design considerations are site-specific . Site constraints include zoning requirements, height restrictions, and restrictions on the location of air intake louvers (the louvers can present noise problems). The addition of PTA will also require system hydraulics changes such as restaged well pumps, matching of booster pumps to well pumps, and repumping of the treated water to the distribution system.

In general, the temperature of the water within the column is close to the temperature of the influent water, and therefore it is not necessary to house the tower. In one installation, air and water temperatures were collected during winter operation to demonstrate the small drop in water temperature even under air temperatures well below freezing (see Figure 5-26). In cold climates, blowers and pumping equipment may have to be housed to prevent freezing. Housing this equipment also provides the additional benefits of increased security, reduced noise, and less frequent maintenance.

The column itself can be made of a variety of materials, including fiberglass-reinforced plastic, aluminum, stainless steel, and concrete. The column's internal components include a mist eliminator to prevent water from escaping through the air exit ports, a liquid distributor to separate the water flow into many small streams, a support grid for the packing material, and the packing material itself.

The air flow system must draw ambient air that is free of contamination and must discharge air that meets discharge regulations. Some states enforce discharge rate regulations in lb/hr or lb/day. Others use modeling to determine the aeration system's contribution to ambient concentrations of contaminants. If an aeration system violates ambient discharge regulations, column modifications such as increased height, air flowrate, and exit velocity can

Figure 5-22. Catenary grid system.

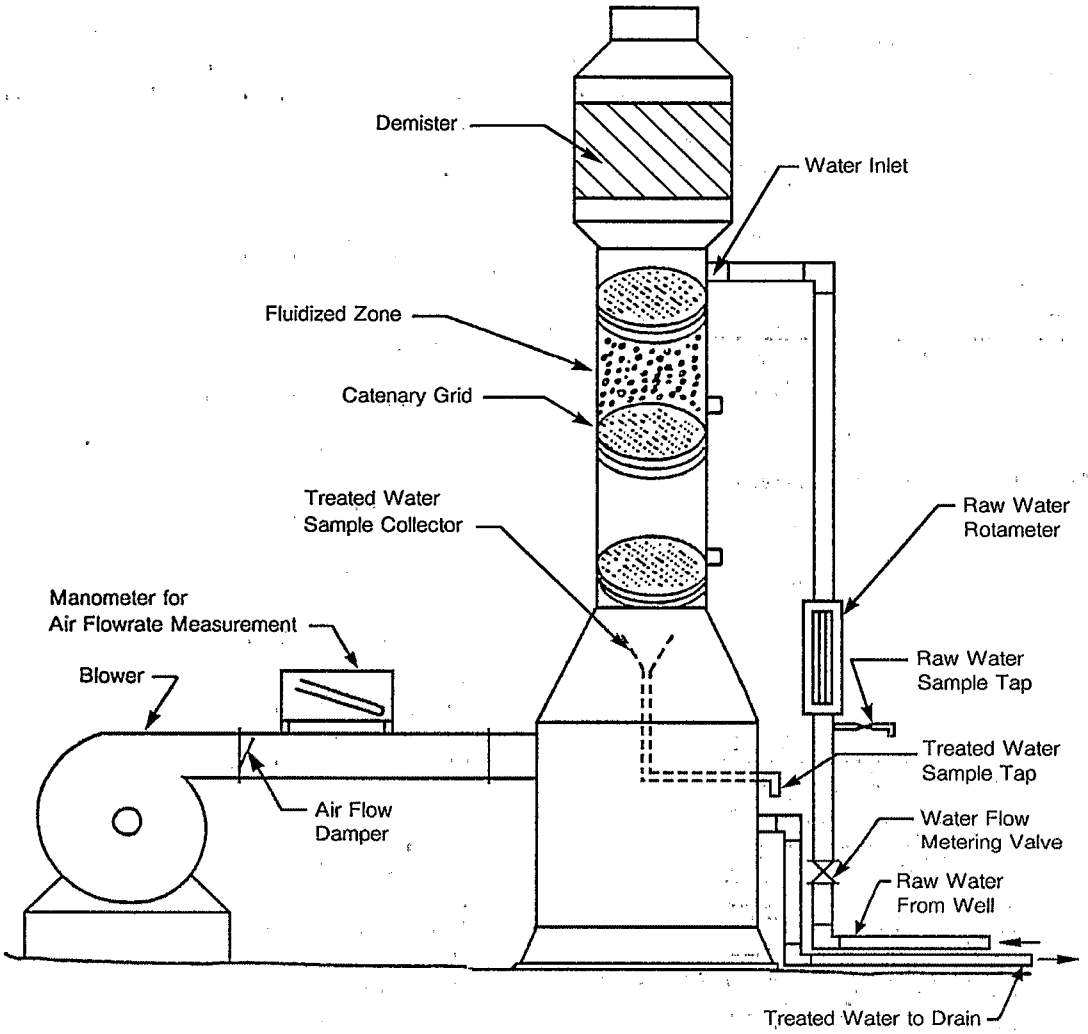


Figure 5-23. Higee system.

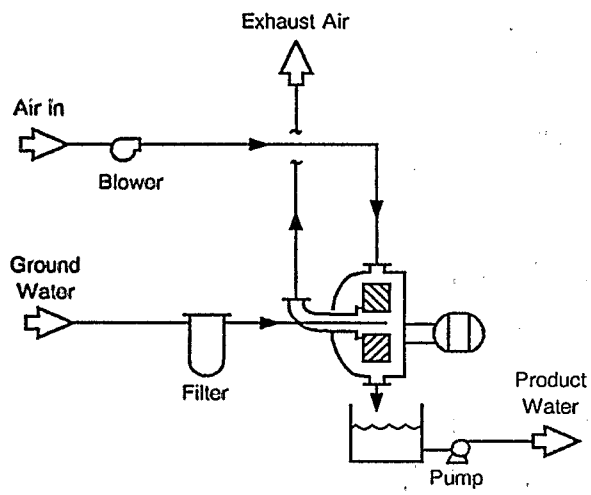


Figure 5-24. Effect of compound on packed column design.

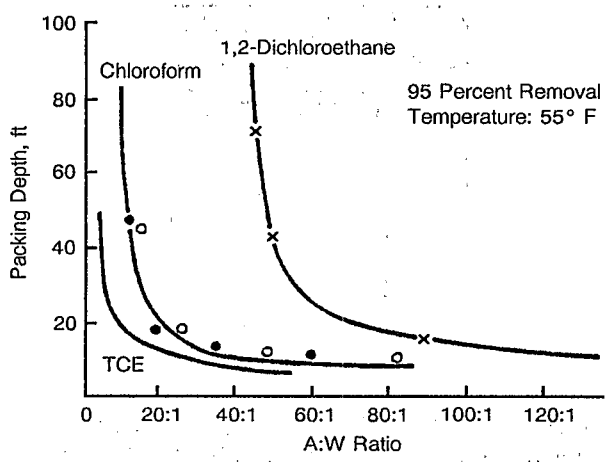


Figure 5-25. Packing height vs. removal (TCE).

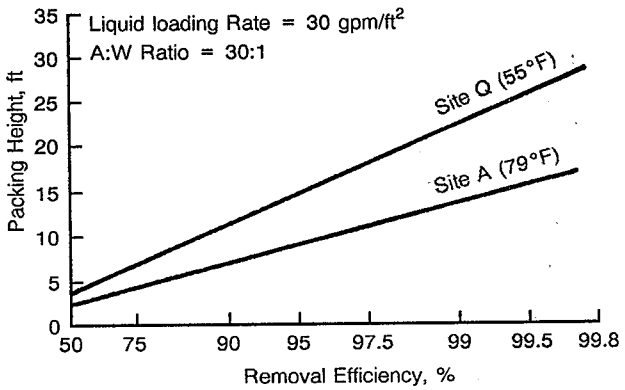
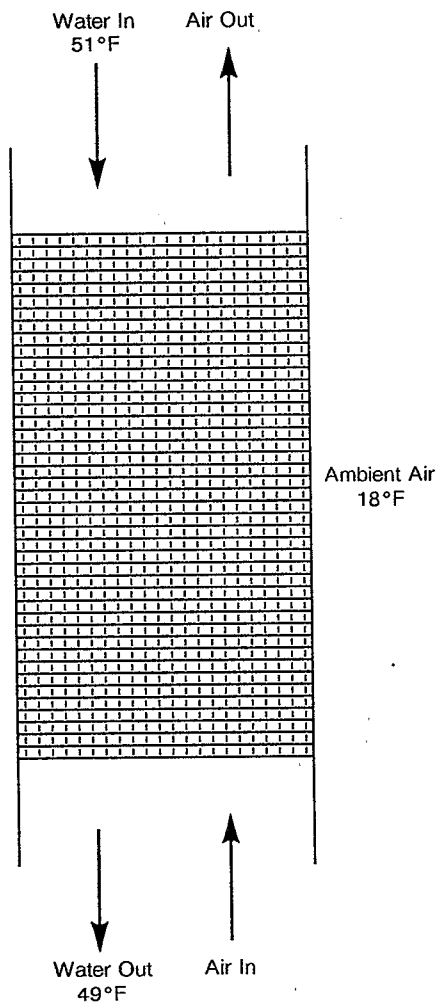


Figure 5-26. Low temperature on aeration.



be used to propel the exit air higher into the atmosphere, thus allowing greater dilution and dispersion to reduce contaminant concentrations near the ground. If this does not work, or if a system violates discharge rate regulations, the exit air can be treated with a vapor phase carbon system, as shown in Figure 5-27. This system passes the exit air through a carbon contactor to trap the organic contaminants. Before entering the contactor, the air passes through a heating element to reduce its relative humidity because high humidity competes for carbon sites with the organics.

To prevent clogging of the packing in the column, pretreatment may have to be incorporated into the system. Causes for clogging include high calcium, iron, and solids concentrations as well as biological growth.

In some cases, the treated water may be made more corrosive by aeration because the aeration process increases the water's dissolved oxygen (DO) concentration. However, since aeration also reduces the treated water's CO_2 concentration, the increased DO is often balanced out. If necessary, corrosivity can be reduced with corrosion inhibitors.

5.3.2.5 Cost of PTA

The basic capital cost components of a PTA system include the column structure and internals, the packing, blower(s), clearwell, booster pump(s), and any associated piping. Site-specific costs can also be added to these costs, including the following:

- Raw water holding tank
- Restaged well pump
- Blower building
- Chemical facility
- Noise control installation
- Air emissions control

Figure 5-28 shows the relationship between system size (in terms of water flowrate) and capital costs for PTA systems. No clear trend emerges because column height, rather than water and air flowrate, is the main determinant of PTA capital cost. Therefore, column height, rather than system size in flowrate, should be used to estimate PTA capital costs.

Figure 5-29 shows the relationship between system size (in flowrate) and O & M costs. Here, a linear relationship occurs because flow rate is the main determinant of O & M cost. Thus, an estimate of system size will give a relatively good estimate of O&M cost.

Table 5-11 summarizes the relative costs for removal of certain organic contaminants by PTA.

5.3.2.6 Case Study: Packed Tower Aeration

This case study describes the use of packed tower aeration to treat VOC contamination of ground water in Scottsdale, AZ (11). The water supply system

Figure 5-27. Vapor-phase carbon system for treatment of aeration exhaust air.

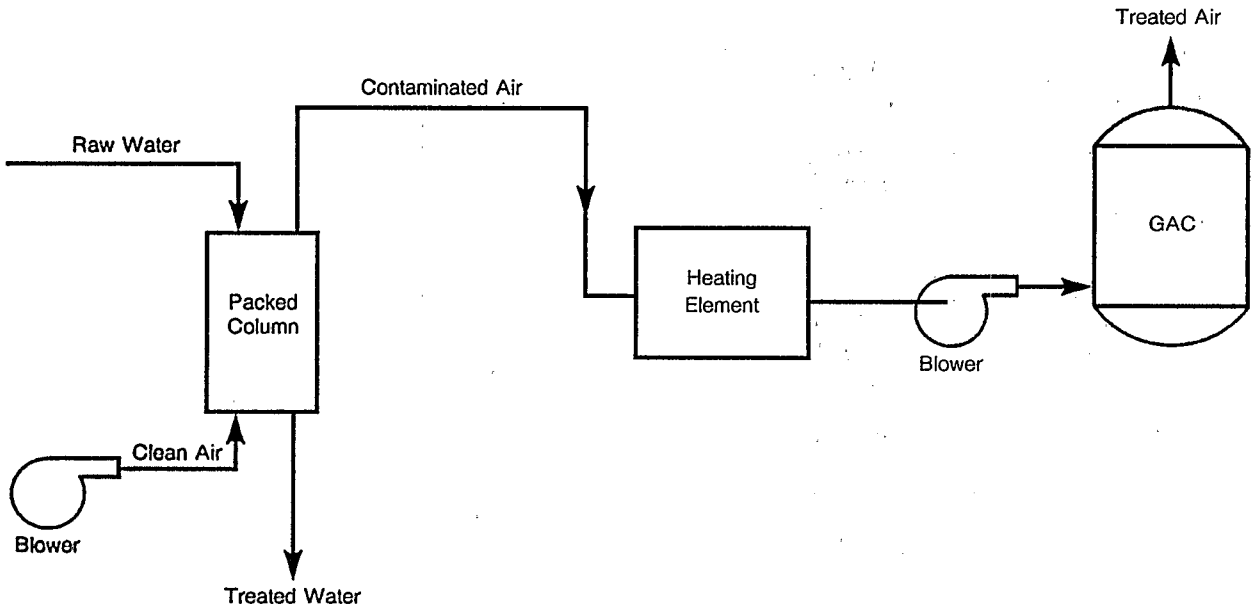


Figure 5-28. Capital costs for packed column systems.

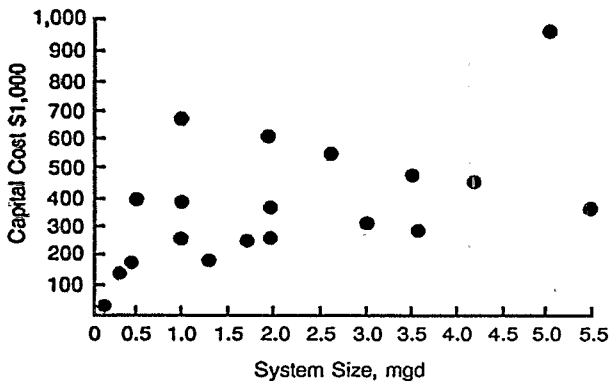


Figure 2-29. Annual O & M costs for packed columns.

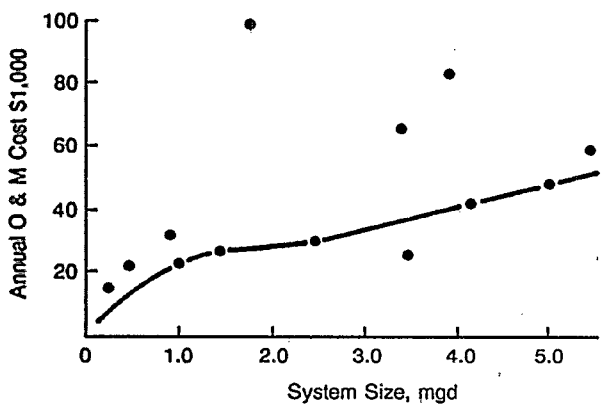


Table 5-11. Relative Costs for Removal by Aeration

Vinyl chloride	Least Costly to Remove
PCE	
TCE	
Carbon tetrachloride	
1,2-Dichloroethane	
DBCP	Most Costly to Remove

consisted of 24 wells with a combined capacity of 40 MGD. Two wells were contaminated with TCE, one with levels of 18-200 µg/L and the other with levels of 5-43 µg/L.

A packed tower aeration system was constructed that had the following design characteristics: 1,200 gpm flow, 12-ft packing height, 50:1 A:W ratio, and 10 ft column diameter. Effluent TCE levels of 0.5 to 1.2 µg/L were achieved, making the removal efficiency above 99 percent.

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Chapter 6

Risk Communication

A safe drinking water supply is very important to the public, and any drinking water emergency, perceived or real, will focus a lot of attention on the people managing drinking water supplies. Therefore, this chapter describes risk communication with the public, primarily through the media. General background on the media is provided and then specific steps to take when relating to the media are outlined

6.1 What You Need to Know About the Media

First, it important to realize that the media can actually be your ally in a drinking water crisis. They can quickly disseminate crucial information to the public, such as where to obtain bottled water. If their coverage of the crisis is accurate, they can also allay unfounded fears and inspire confidence

On the other hand, there are several disadvantages of the media's coverage of environmental risk. Perhaps the most important is shallowness. In newspapers and radio and television news, stories must be brief and easily understood by a very broad spectrum of people: this condensation and simplification of often very complicated situations can misrepresent the truth.

Further, most reporters are generalists (or "general assignment" reporters). Such a person has very little college-level science background and very little time to complete a story. Media deadlines are extremely tight, with one reporter juggling multiple stories in one day. Thus, a typical general assignment reporter does not have the inclination or time to dig up the background information necessary to fully understand a drinking water emergency. All of these factors add up to a rushed, somewhat unprepared reporter arriving at you door. You will serve as this reporter;s sole source of key scientific background information (more on this later).

It is also important to note that the relative degree of environmental risk (in terms of the actual human toxicity vis-a-vis other daily risks and exposure routes) is usually not of great interest to the reporter. Typically, after having established that the contaminant in question is, for example, carcinogenic to laboratory animals, a reporter will move on to other questions such as who caused the contamination, who will clean it up, and how much it will cost.

Another major disadvantage of the media's coverage of environmental risk is sensationalism. The public craves bad news, not good news. News stories must be produced every day and a reporter's natural tendency is to amplify the seriousness of your drinking water emergency, even if the actual problem may be relatively minor.

Another important media practice is the personalizing of stories. A contamination emergency may elicit questions such as "Would you want you family to drink this water?"

6.2 Handling the Media

You can use several specific strategies in relating to the media. A first step is to select a primary and alternate spokesperson from within your organization, and have the telephone receptionist direct all media inquiries to these two people. Since reporters' questions can seem combative, a spokesperson must be calm under stress and capable of speaking well in public. This spokesperson must have access to all of the pertinent in-house information.

6.2.1 Overcoming Shallowness

To overcome the media's potential shallowness, you must educate the reporter. Use lots of facts and be prepared to clearly explain such principles of risk assessment as the use of animal data, different exposure routes, and the assumptions that underlie dose-response curves.

If necessary, use simple visual aids such as paper flip charts. In such material, make sure that all units are presented consistently. Don't express a single contaminant in three different (yet mathematically equivalent) ways: for example, 1 mg/L, 1 ppm, and 1,000 µg/L. Explain any acronyms used, such as MCL (maximum contaminant level).

If you're lucky enough to be covered by a specialized "beat" reporter, try to cultivate this person. Perhaps you can meet with this person to outline the scientific and regulatory background the public needs to fully understand drinking water issues.

6.2.2 Overcoming Sensationalism

To overcome sensationalism, appeal to the reporter's values. Most reporters (as well as water utility employees) adhere to a strict code of professional ethics. If you make it clear that you are presenting the facts in as clear and straightforward a manner as possible, the media will treat you fairly in return. When answering questions, never lie and never guess. If necessary, offer to get back to a reporter for questions that cannot be answered immediately.

Don't withhold information and allow a story to leak out gradually, thereby creating the impression that hidden wrongdoing in inexorably coming to light in the press. Rather, present as much information as possible in the initial interviews.

6.2.3 Conducting Interviews

In interviews, remember that, for all practical purposes, there is no such thing as an "off the record" comment. Assume all microphones are turned on. When preparing for this interview, decide in advance what you want to communicate, and stress and repeat it until you are satisfied that the reporters have gotten your message. Be firm but not hostile.

Don't forget practical considerations such as setting aside space and telephones for the reporters.

6.3 Conclusion

In summary, prepare for the interview, educate the media when necessary, and be as forthcoming as possible. Finally, after having accommodated the media in a professional manner, remember to stop speaking. Don't be lured into speaking about subjects about which you have limited knowledge.

As a final aid to the risk communicator, Table 6-1 provides a crisis communication checklist and Table 6-2 summarizes the 10 most common mistakes of crisis communication.

Table 6-1. Crisis Communication Checklist

--Be prepared. Review the facts
--Be honest. Tell the truth.
--Anticipate likely questions.
--Consider what the audience wants to know.
--Decide what you want to say.
--Consider if there are things you do not want to discuss.
--Compose concise, accurate answers.
--Avoid jargon
--Don't fly by the seat of your pants; you might crash.
--If you do not know the answer to a question, do not guess.
--Stay calm. Do not lose your cool.
--Speak up. Do not mumble.
--Be assertive, not arrogant.
--Do not argue with reporters, bystanders, activists. Do not show fright
--Avoid flight
--Counter false assumptions in questions.
--When finished, remember to stop.

Source: Rowan and Blewitt Environmental Consultants, Washington, DC.

Table 6-2. Ten Common Mistakes in Crisis Communication

The first mistake is to underestimate the importance of the media at the onset of a crisis. The media's dissemination of information is crucial. In most serious emergencies, the presence of photographers and reporters is automatic. If early on the press feels like an unwelcomed guest, it returns the cool reception by heating up the rhetoric.

The second mistake is to fail to understand the media's need for regular information updates. In this day of mini-cams, failure to provide concise factual updates can result in wild speculation.

The third mistake is to fail to establish a central place where information can be coordinated. Without one, reporters may wander and talk with uninformed bystanders. Communications must be coordinated to ensure accurate information.

The fourth mistake is to fail to take charge. The spokesperson must both answer questions and disseminate information.

The fifth mistake is to fail to anticipate likely questions. The basic questions of journalism-who, what, when, how-can be expected. Remember, people want to know, "Is it safe now?"

The sixth mistake is to be lured into hypothetical questions.Avoid "what-if" questions.When asked to predict, stick to the facts and make projections, if any, based on what is known.

The seventh mistake is to accidentally use emotionally charged or sensational language in response to questions. Don't contribute to hype.

The eight mistake is to assign blame for an accident. It's likely that litigation will last for years anyway, so keep personal opinions in check.

The ninth mistake is to try to distort the facts.

The tenth mistake is to let questions get under your skin. Show by your demeanor and candor that you will cooperate with courteous journalists. Keep cool.

Source: Rowan and Blewitt Environmental Consultants, Washington, DC.

Primary and Secondary Drinking Water Regulations

Table A-1. Primary Drinking Water Regulations

Contaminant	Health Effects	MCL, mg/L	Sources
Microbiological			
Total coliforms (coliform bacteria, fecal coliform, streptococcal, and other bacteria)	Not necessarily disease producing themselves but can be indicators of organisms that cause assorted gastroenteric infections: dysentery, hepatitis, typhoid fever, chlolera, and others. Also interfere with disinfection process	1 per 100 mL*	Human and animal fecal matter
Turbidity	Interferes with disinfection	1-5 Tu	Erosion, runoff, discharge
Inorganic Chemicals			
Arsenic	Dermal and nervous system effects	0.05	Geological, pesticide residues, industrial waste, and smelter operation
Barium	Circulatory	1.0	Geological
Cadmium	Kidney effects	0.01	Geological, mining, and smelting
Chromium	Liver/kidney effects	0.05	Industrial
Lead	Central and peripheral nervous system damage, kidney effects, highly toxic to infants and pregnant women	0.05**	Leaches from lead pipe and lead based solder pipe joints
Mercury	Central nervous system disorders, kidney effects	0.002	Manufacturing, fungicides, geological
Nitrate	Methemoglobinemia ("blue-baby syndrome")	10	Fertilizer, sewage, feedlots, geological
Selenium	Gastrointestinal effects	0.01	Geological, mining
Silver	Skin discoloration (argyria)	0.005	Geological, mining
Fluoride	Skeletal damage	4	Geological additive to drinking water, toothpaste, and food processed with fluorinated water
Organic Chemicals			
Endrin	Numerous system/kidney effects	0.0002	Insecticide used on cotton, small grains, orchards (cancelled)
Lindane	Numerous system/liver effects	0.004	Insecticide used on seed and soil treatments, foilage applications, wood protection
Methoxychlor	Numerous system/kidney effects	0.1	Insecticide used on fruit trees and vegetables

Table A-1. (continued)

Contaminant	Health Effects	MCL, mg/L	Sources
Organic Chemicals (continued)			
2,4-D	Liver/kidney effects	0.1	Herbicide used to control broad-leaf weeds in agriculture, used on forests, range, pastures, and aquatic environments.
2,4,5-TP (Silvex)	Liver/kidney effects	0.01	Herbicide, canceled in 1984
Toxaphene	Cancer risk	0.005	Insecticide used on cotton, corn, grain
Benzene	Cancer	0.005	Fuel (leaking tanks), solvent commonly used in manufacture of industrial chemicals, pharmaceuticals, pesticides, paints, plastics
Carbon tetrachloride	Possible cancer	0.005	Common in cleaning agents, industrial wastes from manufacture of coolants
p-Dichloropenzene	Possible cancer	0.075	Used in insecticides, moth balls, air deodorizers
1,2-Dichloroethane	Possible cancer	0.005	Used in manufacture of insecticides,gasoline
1,1-Dichloroethylene	Liver/kidney effects	0.007	Used in manufacture of food wrappings, synthetic fibers
1,1,1-Trichlorothane	Nervous system effects	0.20	Used in manufacture of food wrappings, synthetic fibers
Trichloroethylene (TCE)	Possible cancer	0.005	Waste from disposal of dry cleaning material and manufacture of pesticides, paints, waxes and varnishes, paint stripper, metal degreaser
Vinyl chloride	Cancer risk	0.002	Polyvinyl pipes (PVC) and solvents used to join them, industrial waste from manufacture of plastics and synthetic rubber
Total trihalomethanes (TTHM) (chloroform, bromoform, bromodichloromethane, dibromochloromethane)	Cancer Risk	0.10	Primarily formed when surface water containing organic matter is treated with chlorine
Radionuclides			
Gross alpha particle activity	Cancer risk	15 pCi/L	Radioactive waste, uranium deposits
Gross beta particle activity	Cancer risk	4 mrem/year	Radioactive waste, uranium deposits
Radium 226 & 228	Bone cancer risk	5 pCi/L	Radioactive waste, geological

*The final rule of June 29, 1989 (effective December 31, 1990) based compliance on the presence/absence of total coliform rather than density per unit volume as per current regulation.

**The proposed rule of August 18, 1988 proposed an MCL for lead of 0.005 mg/L for water leaving the treatment plant. In addition, another lead standard of 0.01 mg/L was proposed for an average of a representative number of samples from customers' taps.

Table A-2. Secondary Drinking Water Regulations

Contaminant	Limit	Effect
pH	6.5-8.5	Water should not be too acidic or too basic
Chloride	250 mg/L	Taste and corrosion of pipes
Copper	1 mg/L	Taste and staining of porcelain
Foaming agents	0.5 mg/L	Aesthetic
Sulfate	250 mg/L	Taste and laxative effects
Total dissolved solids (TDS)	500 mg/L	Taste and possible relation between low hardness and cardiovascular disease, also an indicator of corrosivity (related to lead levels in water), can damage plumbing and limit effectiveness of soaps and detergents
Zinc	5 mg/L	Taste
Fluoride	2 mg/L (plus notification)	Dental fluorosis (discoloration of teeth)
Color	15 color units	Aesthetic
Corrosivity	Noncorrosive	Aesthetic and health related (in relation to leaching of materials such as lead from pipes)
Iron	0.3 mg/L	Taste
Manganese	0.05 mg/L	Taste
Odor	3 threshold odor number	Aesthetic

Appendix B

Health Advisory Documents for Aldicarb, Atrazine, Trichloroethylene, and Vinyl Chloride

I. Introduction

The Health Advisory (HA) program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist federal, state and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for One-Day, Ten-Day, Longer-Term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. Current understanding of the biological mechanisms involved in cancer is insufficient to prove that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

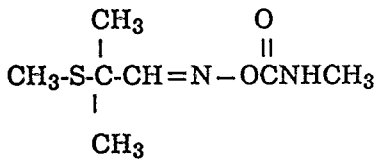
These HAs are based on information presented in ODW's draft Health Effects Criteria Documents (CDs). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161. The toll-free number is (800) 336-4700; the regular number is (703) 487-4650.

II. ALDICARB (Sulfoxide and Sulfone)

A. General Information and Properties

CAS No.: 116-06-3

Structural Formula:



2-methyl-2-(methylthio)propionaldehyde 0-methylcarbamoyl oxime

Synonyms: Temik®

Use: Pesticide (nematocide, acaracide)

Properties: (U.S. EPA, 1985)

Chemical formula	$C_7H_{14}O_2N_2S$
Molecular weight	190.3
Physical state (room temp.)	White crystals
Boiling point	Decomposes above 100°C
Melting point	100°C
Density	---
Vapor pressure	0.05 torr at 20°C
Specific gravity	1.195 at 25°C
Water solubility	6 g/L (room temp.)
Taste threshold (water)	---
Odor threshold (water)	---
Odor threshold (air)	Odorless to light sulfur smell
Conversion factor	---

Occurrence

- EPA estimated that aldicarb production ranged from 3.0 to 4.7 million lb per year during 1979-1981. Aldicarb is applied both to the soil and directly to plants.

- Aldicarb is considered to be moderately persistent as a pesticide. Aldicarb is metabolized rapidly by plants after application to sulfoxide and sulfone. Once in the soil, aldicarb is degraded by both aerobic and anaerobic bacteria. Aldicarb has a soil half- life of 2 to 6 weeks, with residual levels found up to 6 to 12 months later. Aldicarb in pond water was reported to degrade more rapidly, with a half-life of 5 to 10 days. Aldicarb is expected to hydrolyze slowly over months or years in most ground and surface waters. Aldicarb and its sulfoxide and sulfone degradation products do not bind to soil or sediments and have been shown to migrate extensively in soil. Aldicarb does not bioaccumulate to any significant extent.

- Aldicarb has been reported to occur widely in ground water at levels in the low ppb range. New York, Florida, Wisconsin and Maine, among other states, have restricted the use of aldicarb based on its potential for ground-water contam-ination. Aldicarb has not been measured in Agency surveys of drinking water, and estimates of national exposures are unavailable. Because of aldicarb's relatively rapid degradation rate, it is expected to occur more often in ground waters than surface waters (U.S. EPA, 1983).

- Monitoring of aldicarb residues on foods have found only occasional low levels of the pesticide and its metabolites (U.S. FDA, 1984). The Agency has set limits for residues that would result in an adult receiving a daily dose of 100 µg/kg a day. For drinking water exposures to exceed this dose, concentrations that need to exceed 50 µg/L.

B. Pharmacokinetics

Absorption

- Aldicarb, as well as its sulfoxide and sulfone metabolites, has been shown to be absorbed readily and almost completely through the gut in a variety of mammalian and nonmammalian species (Knaak et al., 1966; Andrawes et al., 1967; Dorough and Ivie, 1968; Dorough et al., 1970; Hicks et al., 1972; Cambon et al., 1979).

- Dermal absorption of aldicarb has been demonstrated in rabbits (Kuhr and Dorough, 1976; Martin and Worthing, 1977) and rats (Gaines, 1969), and would be expected to occur in unprotected humans in manufacturing and field application settings.

Distribution

- Aldicarb is distributed widely in the tissues of Holstein cows when administered in feed (Dorough et al., 1970). Highest residues were found in the liver. When aldicarb was administered at a lower level, residues were detected only in the liver.

- In rats administered aldicarb orally, residues were found in all 13 tissue types analyzed. Hepatic residue levels were similar to those of many other tissues (Andrawes et al., 1967).

- Aldicarb, in a 1:1 molar ratio of the parent compound to sulfone, administered orally to laying hens in a single dose or for 21 consecutive days, resulted in similar patterns of distribution with the liver and kidneys as the main target organs (Hicks et al., 1972). Residues also were present in both the yolks and whites of the eggs laid by these hens.

Metabolism

- The metabolism of aldicarb involves both hydrolysis of the carbamate ester and oxidation of the sulfur to sulfoxide and sulfone derivatives, which have been shown to be active cholinesterase inhibitors (Andrawes et al., 1967; Bull et al., 1967).

- Metabolic end products of aldicarb detected in both the milk and urine of a cow included the sulfoxides and sulfones of the parent compound, oxime and nitrile, as well as a number of unknown metabolites (Dorough and Ivie, 1968).

Excretion

- Elimination of aldicarb and its metabolism products occurs primarily via the urine, as demonstrated in rats (Knaak et al., 1966), cows (Dorough and Ivie, 1968), and chickens (Hicks et al., 1972).

- Excretion of aldicarb via the lungs as $C0_2$ has been demonstrated as a minor route in rats (Knaak et al., 1966) and in the milk of cows (Dorough and Ivie, 1968).

- Excretion of aldicarb is relatively rapid, with reported 24-hour elimination values in rats and cows of approximately 80% to 90% of the administered dose (Knaak et al., 1966; Dorough and Ivie, 1968).

C. Health Effects

Humans

- In two related incidents in 1978 and 1979, ingestion of cucumbers presumed to contain aldicarb at about 7 to 11 ppm resulted in complaints of diarrhea, abdominal pain, vomiting, nausea, excessive perspiration, dyspnea, muscle fasciculation, blurred vision, headaches, convulsions and/or temporary loss of limb function in a total of fourteen residents of a Nebraska town (CDC, 1979; Goes et al., 1980). Onset of symptoms occurred within 15 minutes to 2.25 hours, and they continued for approximately 4 to 12 hours.

- Industrial exposure by a man bagging aldicarb for one day resulted in nausea, dizziness, depression, weakness, tightness of chest muscles, and decreases in plasma and red blood cell cholinesterase activity (Sexton, 1966). The symptoms lasted more than 6 hours, but the subject returned to work the following day without symptoms.

- In a laboratory study, four adult males orally administered aldicarb at 0.1 mg/kg experienced a variety of cholinergic symptoms, including malaise, weakness in their limbs, pupil contraction and loss of photoreactivity, epigastric cramps, sweating, salivation, nausea, vomiting, and "air hunger" (Haines, 1971). These symptoms did not occur at 0.025 or 0.05 mg/kg. Depression of cholinesterase activity occurred in a dose-dependent manner, with values as low as 25% of the control value measured in two subjects dosed at 0.1 mg/kg.

- Fiore et al. (1986) studied the effect of chronic exposure to aldicarb-contaminated ground-water on the human immune function. The study was performed on women between the ages of 18 to 70. A group of twenty-three women were exposed to low levels of aldicarb (<61 ppb) and another group of 27 women were unexposed. The results of this study suggest a potential association between exposure to aldicarb and abnormalities in T-cells. However, the statistical analysis of these data indicates that additional studies are needed before further conclusions can be made on the effect of aldicarb on the immune function.

Animals

Short-Term Exposure

- NAS (1977) stated that the acute toxicity of aldicarb is probably the greatest of any widely used pesticide.

- Reported oral LD_{50} values for aldicarb administered to rats in corn or peanut oil range from about 0.65 to 1 mg/kg (Weiden et al., 1965; Gaines, 1969). Females appear to be more sensitive than males. The oral LD_{50} in mice is 0.3 to 0.5 mg/kg (Black et al., 1973).

- Oral LD_{50} values for aldicarb were higher when using a vehicle other than corn or peanut oil. Weil (1973) reported an oral LD_{50} of 7.07 mg/kg in rats administered aldicarb as dry granules. Carpenter and Smyth (1965) reported an LD_{50} of 6.2 mg/kg in rats administered aldicarb in drinking water.

- Dermal toxicity also is high with 24-hour LD_{50} values of 2.5 and 3 mg/kg reported for female and male rats, respectively (Gaines, 1969) and 5 mg/kg in rabbits (Weiden et al., 1965).

- The principal toxic effect of aldicarb and its sulfoxide and sulfone metabolites in rats has been shown to be cholinesterase inhibition (Weil and Carpenter, 1963; Nycum, 1968; Weil, 1969).

- Feeding studies of short duration (7 to 15 days) have been conducted by various authors using aldicarb and/or its sulfone and sulfoxide. Statistically significant decreases in

cholinesterase activity were observed in rats at dosage levels of 1 mg/kg/day (the approximate LD_{50} in rats) (Nycum and Carpenter, 1970) and at 2.5 mg/kg/day in chickens (Schlinke, 1970). The latter dosage also resulted in some lethality in test animals.

- A NOAEL has been determined for a mixture of aldicarb oxidation products based on data reported by Mirro et al. (1982), who administered aldicarb sulfone and sulfoxide in a 1:1 ratio in the drinking water of young rats for 8 to 29 days. Doses ranged up to 1.67 mg/kg/day for males and 1.94 mg/kg/day for females. Based on statistically significant reductions in cholinesterase activity in brain, plasma, and red blood cells (RBC) at higher dosage levels, a NOAEL of 0.12 mg/kg/day was determined.

Long-Term Exposure

- High dosages of aldicarb sulfoxide (0.25 to 1.0 mg/kg/day) or aldicarb sulfone (1.8 to 16.2 mg/kg/day) administered in the diets of rats for 3 or 6 months resulted in decreases in cholinesterase activity in plasma, RBCs, and brain (Weil and Carpenter, 1968a,b). No increases in mortality or gross or microscopic histopathology were noted in any group, however. Data derived from the lower dosage levels of this study have been used by the World Health Organization Committee on Pesticide Residues (FAO/WHO, 1980) to derive a NOAEL of 0.125 mg/kg/day for aldicarb sulfoxide in the rat. The NOAEL for aldicarb sulfone alone was 0.6 mg/kg/day.
- Aldicarb administered for 2 years in the diets of rats or dogs at levels up to 0.1 mg/kg/day resulted in no significant increase in adverse effects based on a variety of toxicologic end points (Weil and Carpenter, 1965, 1966a). In another 2-year study, levels of up to 0.3 mg/kg/day resulted in no adverse affects in rats (Weil, 1975).
- Feeding studies using aldicarb sulfoxide at 0.6 mg/kg/day for 2 years resulted in an increase in the mortality rates of female rats (Weil, 1975).

Reproductive Effects

- No reproductive effects have been demonstrated to result from the administration of aldicarb to rats (Weil and Carpenter, 1964, 1974).

Developmental Effects

- No teratogenic effects have been demonstrated from the administration of aldicarb in rabbits (IRDC, 1983) or chickens (Proctor et al., 1976).
- No adverse effects on milk production were observed in studies of lactating cows or rats (Dorough and Ivie, 1968; Dorough et al., 1970).
- Statistically significant inhibition of acetylcholinesterase activity has been demonstrated in the liver, brain, and blood of rat fetuses when their mothers were administered aldicarb by gastric intubation on day 18 of gestation (Cambon et al., 1979). These changes were seen at doses of 0.001 mg/kg and above and were manifested within 5 minutes of the administration of 0.1 mg/kg.

Mutagenicity

- Aldicarb has not been demonstrated to be conclusively mutagenic in Ames bacterial assays or in a dominant lethal mutagenicity test in rats (Ercegovich and Rashed, 1973; Weil and Carpenter, 1974; Godek et al., 1980).

Carcinogenicity

- Neither aldicarb nor its sulfoxide or sulfone metabolite have been demonstrated to increase significantly the incidence of tumors in mice or rats in feeding studies (Weil and Carpenter, 1965; NCI, 1979). Bioassays with aldicarb in which rats and mice were fed either 2 or 6 ppm in the diet for 103 weeks revealed no tumors that could be attributed solely to aldicarb administra-tion (NCI, 1979). It was concluded that, under the conditions of the bioassay, technical grade (99+%) aldicarb was not carcinogenic to F344 rats or $B6C3F_1$ mice of either sex. A 2-year feeding study reported by Weil and Carpenter (1965) also produced no statistically significant increase in tumors over controls when rats were administered aldicarb at equivalent doses of 0.005, 0.025, 0.05, or 0.1 mg/kg bw/day in the diet. Weil (1975) similarly reported no adverse effects in Greenacres Laboratory Controlled Flora rats fed aldicarb at 0.3 mg/kg bw/day for 2 years.
- In the only skin-painting study available to date, Weil and Carpenter (1966b) found aldicarb to be noncarcinogenic to male C3H/H3J mice under the conditions of the experiment.
- Intraperitoneally administered aldicarb did not exhibit transforming or tumorigenic activity in a host-mediated assay using pregnant hamsters and nude (athymic) mice (Quarles et al., 1979).

D. Quantification of Toxicological Effects

The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (\text{BW})}{(\text{UF}) \times (\_\_ \text{L/day})}$$

$$= \_\_\_\_\_ \text{mg/L} (\_\_\_\_\_ \mu\text{g/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, or 1,000), in accordance with NAS/ODW guidelines.

____L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

The available data suggest that the appearance of cholinergic symptoms indicative of cholinesterase enzyme inhibition is the most sensitive indicator the effects of exposure to aldicarb. Adverse health effects appear to be related primarily to the depression of cholinesterase activity, as no other biochemical, morphological, reproductive, mutagenic or carcinogenic effects have been reported, even after chronic dosing.

Given the nature of the primary toxicity (rapidly reversible cholinesterase inhibition) of aldicarb and its oxidative metabolites/degradation products, it is apparent that the same NOAEL can be used as the basis for the derivation of acceptable levels over virtually any duration of exposure. In addition, the Health Advisories calculated in this document are appropriate for use in circumstances in which sulfoxide and/or sulfone may be the substance(s) present in a drinking water sample. Depending upon the analytical method applied, it may not be possible to characterize specifically the residue(s) present. By establishing Health Advisories based on data from valid studies with the most potent of the three substances, assurance is greater that the guidance is protective to human health.

As described above, a NOAEL of 0.125 mg/kg bw/day can be determined from the Weil and Carpenter (1968b) and Mirro et al. (1982) studies. From this NOAEL, all HA values can be determined for aldicarb, aldicarb sulfoxide, or a mixture of the sulfoxide and sulfone metabolite (however, if the only contaminant is sulfone and a less conservative value is thus appropriate, the NOAEL for the sulfone, 0.6 mg/kg/day, as determined in the Weil and Carpenter (1986) study, can be used).

One-Day Health Advisory

For the 10-kg child:

$$One\text{-}Day\ HA = \frac{(0.125\ mg/kg/day)\,(10\ kg)}{(100)\ (1\ L/day)}$$

$$= 0.012\ mg/L\ \ (10\ \mu g/L)$$

where:

0.125 mg / kg/day = NOAEL, based on lack of significant decreases in cholinesterase activity in rats.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

(NOTE: Using the NOAEL for the sulfone alone, the HA value for this metabolite would be 0.06 mg/L (60 µg/L) if sulfone is the only contaminant.)

Ten-Day Health Advisory

Since aldicarb is metabolized and excreted rapidly (>90% in urine alone in a 24-hour period following a single dose), the One- and Ten-Day HA values would not be expected to differ to any extent. Therefore, the Ten-Day HA will be the same as the One-Day HA (10 µg/L).

Longer-Term Health Advisory

For the 10-kg child:

$$Longer\text{-}term\ HA = \frac{(0.125\ mg/kg/day)\ (10\ kg)}{(100)\ (1\ L/day)}$$

$$= 0.012\ mg/L\ (10\ \mu g/L)$$

where:

0.125 mg /kg/day = NOAEL, based on lack of significant decreases in cholinesterase activity in rats.

10 kg = assumed body weight of a child.

100 = uncertainty factor chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

(NOTE: Using the NOAEL for the sulfone alone, the HA value for this metabolite would be 0.06 mg/L (60 µg/L) if the sulfone is only contamiant.)

For the 70-kg adult:

$$Longer-term\ HA = \frac{(0.125\ mg/kg/day)\ (70\ kg)}{(100)\ (2\ L/day)}$$

$$= 0.042\ mg/L\ (40\ \mu g/L)$$

where:

0.125 mg /kg/day	=	NOAEL, based on lack of significant decreases in cholinesterase activity in rats.
70 kg	=	assumed body weight of an adult.
100	=	uncertainty factor chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.
2 L/day	=	assumed daily water consumption of an adult.

(NOTE: Using the NOAEL for the sulfone alone, the HA value for this metabolite would be 0.21 mg/L (210 µg/L) if sulfone is the only contaminant.)

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

As discussed previously, the studies by Weil and Carpenter (1968b) and Mirro et al. (1982) are used in the following calculations. Both studies reflected a NOAEL of 0.125 mg/kg/day.

Step 1: Determination of the RfD

$$RfD = \frac{(0.125\ mg/kg/day)}{(100)} = 0.00125\ mg/kg/day$$

where:

0.125 mg /kg/day	=	NOAEL, based on lack of significant decreases in cholinesterase activity in rats.
100	=	uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

(NOTE: With the NOAEL of 0.6 mg/kg/day for the sulfone alone, the RfD value for this metabolite would be 0.006 mg/kg/day.)

Step 2: Determination of the DWEL

$$DWEL = \frac{(0.00125\ mg/kg/day)\ (70\ kg)}{(2\ L/day)}$$

$$= 0.042\ mg/L\ (40\ \mu g/L)$$

where:

0.00125 mg /kg/day	=	RfD.
70 kg	=	assumed body weight of an adult.
2 L/day	=	assumed daily water consumption of an adult.

(NOTE: With the RfD for sulfone alone, the DWEL for this metabolite would be 0.21 mg/L (210 µg/L)).

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (0.042 mg/L) (20%)
= 0.009 mg/L = 10 µg/L

where:

0.42 mg/L	=	DWEL.
20%	=	assumed contribution of drinking water to total exposure to aldicarb.

(NOTE: With the DWEL for sulfone alone, the Lifetime HA value for this metabolite would be 0.042 mg/L (42 µg/L).

In summary, the Lifetime HA values for aldicarb and its metabolites are as follows:

aldicarb (parent compound)*	: 10 µg/L
aldicarb sulfoxide*	: 10 µg/L
aldicarb sulfone**	: 10 to 42 µg/L

* The HA values for aldicarb and aldicarb sulfoxide are the same because they have similar toxicity, and the effects of the parent compound are likely due to the sulfoxide (and, to a lesser extent, the sulfone).

** The HA value for the sulfone ranges from 10 to 42 µg/L depending on the presence of other aldicarb/aldicarb sulfoxide residues; only if the sulfone metabolite is present alone as a contaminant can the HA value of 42 µg/L be used.

Evaluation of Carcinogenic Potential

- Since aldicarb has been found to be noncarcinogenic under all conditions tested, quantification of carcinogenic risk for lifetime exposures through drinking water would be inappropriate.

- The International Agency for Research on Cancer (IARC) has not classified the carcinogenic potential of aldicarb.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), the Agency has classified aldicarb in Group E: No evidence of carcinogenicity in humans. This category is used for agents that show no evidence of carcinogenicity in at least two adequate animal tests in different species or in both epidemiologic and animal studies.

E. Other Criteria, Guidance, and Standards

- The National Academy of Sciences proposed an ADI of 0.001 mg/kg/day based on 2-year feeding studies in rats and dogs (NAS, 1977). NAS reaffirmed this ADI in 1983 (NAS, 1983).

- In addition, NAS also derived a chronic Suggested-No-Adverse-Effect level (SNARL) of 7 µg/L, using the studies mentioned above with an uncertainty factor of 1,000 (1977). The SNARL is protective of a 70-kg adult, consuming 2 L of water per day and for whom drinking water is assumed to contribute 20 percent of the daily exposure to aldicarb residues.

- EPA's Office of Pesticide Programs established an ADI of 0.003 mg/kg/day based on the data from the 6-month rat feeding study with aldicarb sulfoxide (U.S. EPA, 1981).

- The FAO/WHO proposed ADIs for aldicarb residues of 0-0.001 mg/kg/day in 1979 and 0-0.005 mg/kg/day in 1982 (FAO/WHO, 1979; 1982).

F. Analytical Methods

- Analysis of aldicarb is by a high performance liquid chromatographic procedure used for the determination of N-methyl carbamoyloximes and N- methylcarbamates in drinking water (U.S. EPA, 1984). In this method, the water sample is filtered and a 400-µL aliquot is injected into a reverse phase HPLC column. Separation of compounds is achieved using gradient elution chromatography. After elution from the HPLC column, the compounds are hydrolyzed with sodium hydroxide. The methylamine formed during hydrolysis is reacted with o-pthalaladehyde (OPA) to form a fluorescent derivative that is detected using a fluorescence detector. The method detection limit has been estimated to be approximately 1.3 µg/L for aldicarb.

G. Treatment Technologies

- Techniques that have been used to remove aldicarb from water are carbon adsorption and filtration. Since aldicarb is converted into aldicarb sulfoxide and sulfone, all three compounds must be considered when evaluating the efficiency of any decontamination technique.

- Granular activated carbon (GAC) has been used in two studies of aldicarb removal from contaminated water (Union Carbide, 1979; ESE, 1984). Both studies utilized home water treatment units rather than large-scale water treatment systems. Union Carbide tested the Hytest Model HF-1 water softener in which the ion exchange ion was replaced with 38.5 lb Filtrasorb® 400 (Calgon GAC). The unit was operated at a flow rate of 3 gal/min. Water spiked with 200 ppb or 1000 ppb of a mixture of aldicarb, aldicarb sulfoxide, and aldicarb sulfone in a 10:45:45 ratio was treated. Under these conditions, the total aldicarb residue level was reduced by 99% to 1 ppb for the treatment of 13,500 gallons of water with 200 ppb of residues and 41,500 gallons with 1,000 ppb total residues. No breakthrough of aldicarb occurred. When the study was terminated, the carbon had adsorbed 9 mg aldicarb residue per gram. This value can be compared with an equilibrium loading value of 21 mg per gram of carbon at 16^6 determined using 200 ppb aldicarb residues. In the second study, ESE (1984) did a field study in Suffolk County, NY. Nineteen units using type

CW 12 x 40 mesh carbon were tested. After 38 months of use, breakthrough of aldicarb occurred to levels over 7 µg/L in eight units tested. The range of usage values can be attributed to the fact that the natural well samples contained a variety of adsorbable substances in addition to aldicarb.

- Chlorination also appears to offer the potential for aldicarb removal (Union Carbide, 1979). The company reported that 1.0 ppm free chlorine caused a shift in the ratio of aldicarb, its sulfoxide and its sulfone so that all residues were converted to the sulfoxide within 5 minutes of chlorine exposure. Normal conversion of aldicarb to aldicarb sulfone did not appear to be affected. On stand-ing, the sulfoxide and sulfone decomposed. The decomposition products were not identified. However, should these be nontoxic, then chlorination could be feasible as an aldicarb removal tech-nique.

- Aeration or air stripping, which is commonly used to remove synthetic organic chemicals, is not a good technique for the removal of aldicarb (ESE, 1984). This is because aldicarb has a low Henry's Law constant (2.32 x 10^{-4} atm).

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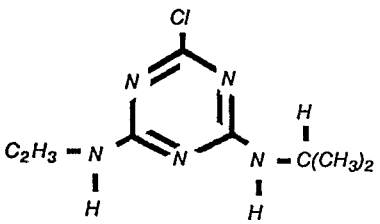
III. ATRAZINE

A. General Information and Properties

CAS No.: 1912-24—9

Structural Formula:



2-Chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine

Synonyms:

- AAtrex; Atranex; Crisatrina; Crisazine; Farmco Atrazine; Griffax; Shell Atrazine Herbicide; Vectal SC; Gesaprim; Primatol (Meister, 1987).

Uses:

- Atrazine over the past 30 years has been the most heavily used herbicide in the U.S. It is used for nonselective weed control on industrial or noncropped land and selective weed control in corn, sorghum, sugar cane, pineapple and certain other plants (Meister, 1987).

Properties: (Meister, 1987; Windholz, 1976)

Chemical formula	$C_8H_{14}ClN_5$
Molecular weight	215.72
Physical state	White, odorless, crystalline solid
Boiling point (25 mm Hg)	–
Melting point	175 to 177°C
Density (20 °C)	1.187
Vapor pressure (20°C)	3.0×10^{-7} mm Hg
Water solubility (22°C)	70 mg/L
Log octanol/Water partition coefficient	2.33 to 2.71
Taste threshold	–
Odor threshold	–
Conversion factor	–

Occurrence

- In a monitoring study of Mississippi River water, atrazine residues were found at a maximum level of 17 ppb; residues were detected throughout the year, with the highest concentrations found in June or July (Newby and Tweedy, 1976).

- Atrazine has been found in 4,123 of 10,942 surface water samples analyzed and in 343 of 3,208 ground-water samples (STORET, 1988). Samples were collected at 1,659 surface water locations and 2,510 ground water locations. The 85th percentile of all non-zero samples was 2.3 µg/L in surface water and 1.9 µg/L in ground water sources. The maximum concentration found in surface water was 2,300 µg/L and in ground water, 700 µg/L. Atrazine was found in surface water of 31 states and in ground water in 13 states. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data are often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

- Atrazine has been found also in ground water in Pennsylvania, Iowa, Nebraska, Wisconsin and Maryland; typical positives were 0.3 to 3 ppb (Cohen et al., 1986).

Environmental Fate

- An aerobic soil metabolism study in Lakeland sandy loam, Hagerstown silty clay loam, and Wehadkee silt loam soils showed conversion of atrazine to hydroxyatrazine, after 8 weeks, to be 38, 40 and 47% of the amount applied, respectively (Harris, 1967). Two additional degradates,

deisopropylated atrazine and deethylated atrazine, were identified in a sandy loam study (Beynon et al., 1972).

- Hurle and Kibler (1976) studied the effect of water-holding capacity on the rate of degradation and found a half-life for atrazine of more than 125 days, 37 days, and 36 days in sandy soil held at 4%, 35%, and 70% water-holding capacity, respectively.

- In Oakley sandy loam and Nicollet clay loam, atrazine had a half-life of 101 and 167 days (Warnock and Leary, 1978).

- Carbon dioxide production was generally slow in several anaerobic soils: sandy loam, clay loam, loamy sand and silt loam (Wolf and Martin, 1975; Goswami and Green, 1971; Lavy et al., 1973).

- ^{14}C-Atrazine was stable in aerobic ground water samples incubated for 15 months at 10 or 25°C in the dark (Weidner, 1974).

- Atrazine is moderately to highly mobile in soils ranging in texture from clay to gravelly sand as determined by soil thin layer chromatography (TLC), column leaching, and adsorption/desorption batch equilibrium studies. Atrazine on soil TLC plates was intermediately mobile in loam, sandy clay loam, clay loam, silt loam, silty clay loam, and silty clay soils, and was mobile in sandy loam soils. Hydroxyatrazine showed a low mobility in sandy loam and silty clay loam soils (Helling, 1971).

- Soil adsorption coefficients for atrazine in a variety of soils were: sandy loam (0.6), gravelly sand (1.8), silty clay (5.6), clay loam (7.9), sandy loam (8.7), silty clay loam (11.6), and peat (more than 21) (Weidner, 1974; Lavy, 1974; Talbert and Fletchall, 1965).

  Soil column studies indicated atrazine was mobile in sand, fine sandy loam, silt loam and loam; intermediately mobile in sand, silty clay loam and sandy loam, low to intermediately mobile in clay loam (Weidner, 1974; Lavy, 1974; Ivey and Andrews, 1964; Ivey and Andrews, 1965).

  In a Mississippi field study, atrazine in silt loam oil had a half-life of less than 30 days (Portnoy, 1978). In a loam to silt loam soil in Minnesota, atrazine phytotoxic residues persisted for more than 1 year and were detected in the maximum depth samples (30 to 42 inches) (Darwent and Behrens, 1968). In Nebraska, phytotoxic residues persisted in silty clay loam and loam soils 16 months after application of atrazine; they were found at depths of 12 to 24 inches. Atrazine phytotoxic residues had a half-life of about 20 days in Alabama fine sandy loam soil, although leaching may partially account for this value (Buchanan and Hiltbold, 1973).

  Under aquatic field conditions, dissipation of atrazine was due to leaching and to dilution by irrigation water, with residues persisting for 3 years in soil on the sides and bottoms of irrigation ditches, to the maximum depth sampled, 67.5 to 90 cm (Smith et al., 1975).

  Ciba-Geigy (1988) recently submitted comments on the atrazine Health Advisory. These comments included a summary of the results of its studies on the environmental fate of atrazine. This summary indicated that laboratory degradation studies showed that atrazine is relatively stable in the aquatic medium under environmental pH conditions and indicated that atrazine degraded in soil by photolysis and microbial processes. The products of degradation are dealkylated metabolites, hydroxyatrazine and nonextractable (bound) residues. Atrazine and the dealkylated metabolites are relatively mobile, whereas hydroxyatrazine is immobile.

  Ciba-Geigy (1988) also indicated that field dissipation studies conducted in California, Minnesota and Tennessee show no leaching of atrazine and metabolites below 6 to 12 inches of soil. The half-lives of atrazine in soil ranged between 20 to 101 days, except in Minnesota where degradation was slow. A forestry degra-dation study conducted in Oregon showed no adverse effects on either terrestrial or aquatic environments. Also, bioconcentration studies have shown low potential for bioaccummulation, with a range of 15 to 77X.

B. Pharmacokinetics

Absorption

Atrazine appears to be readily absorbed from the gastrointestinal tract of animals. Bakke et al. (1972) administered single 0.53-mg doses of ^{14}C-ring labeled atrazine to rats by gavage. Total fecal excretion after 72 hours was 20.3% of the administered dosed; the remainder was excreted in urine (65.5%) or retained in tissues (15.8%). This indicates that at least 80% of the dose was absorbed.

Distribution

- Bakke et al. (1972) administered single 0.53-mg doses of ^{14}C-ring-labeled atrazine to rats by gavage. Liver, kidney and lung contained the largest amounts of radioactivity, while fat and muscle had lower residues than the other tissues examined.

- In a metabolism study by Ciba-Geigy (1983a), the radioactivity of ^{14}C-atrazine dermally applied to Harlan Sprague-Dawley rats at 0.25 mg/kg was distributed to a minor extent to body tissues. The highest levels were measured in liver and muscle at all time points examined; 2.1% of the applied dose was in muscle and 0.5% in liver at 8 hours.

- Khan and Foster (1976) observed that in chickens the hydroxy metabolites of atrazine accumulate in the liver, kidney, heart, and lung. Residues of both 2- chloro and 2-hydroxy moieties were found in chicken gizzard, intestine, leg muscle, breast muscle and abdominal fat.

Metabolism

- The principal reactions involved in the metabolism of atrazine are dealkylation at the C-4 and C-6 positions of the molecule. There is also some evidence of dechlorination at the C-2 position. These data were reported by several researchers as demonstrated below.

- Bakke et al. (1972) administered single 0.53-mg doses of ^{14}C-ring-labeled atrazine to rats by gavage. Less than 0.1% of the label appeared in carbon dioxide in expired air. Most of the radio-activity was recovered in the urine (65.5% in 72 hours), including at least 19 radioactive com-pounds. More than 80% of the urinary radio-activity was identified as 2-hydroxy-atrazine and its two mono-N-dealkylated metabolites. None of the metabolites identified contained the 2-chloro moiety (which may have been removed via hydrolysis during the isolation technique or by a dechlorinating enzyme as suggested by the *in vitro* studies of Foster et al. (1979), who found evidence for a dechlorinase in chicken liver homogenates incubated with atrazine).

- Bohme and Bar (1967) identified five urinary metabolites of atrazine in rats: the two monodealkylated metabolites of atrazine, their carboxy acid derivatives and the fully dealkylated derivative. All of these metabolites contained the 2-chloro group. The *in vitro* studies of Deuterman and Muecke (1974) also found no evidence for dechlorination of atrazine in the presence of rat liver homogenates.

- Similarly, Bradway and Moseman (1982) administered atrazine (50, 5, 0.5, or 0.005 mg/day) for 3 days to male Charles River rats and observed that the fully dealkylated derivative (2-chloro-4,6-diamino-s-triazine) was the major urinary metabolite, with lesser amounts of the two mono-N-dealkylated derivatives.

- Erickson et al. (1979) dosed Pittman-Moore miniature pigs by gavage with 0.1 g of atrazine (80W). The major compounds identified in the urine were the parent compound (atrazine) and deethylated atrazine (which contained the 2-chloro substituent).

- Hauswirth (1988) indicated that the rat metabolism studies taken together are sufficient to show that in the female rat dechlorination of the triazine ring and N-dealkylation are the major metabolic pathways. Oxidation of the alkyl substituents appears to be a minor and secondary metabolic route. The total body half-life is approximately 1 1/2 days. Atrazine and/or its metabolites appear to bind to red blood cells. Other tissue accumulation does not appear to occur.

Excretion

- Urine appears to be the principal route of atrazine excretion in animals. Following the administration of 0.5 mg doses of ^{14}C-ring-labeled atrazine by gavage to rats, Bakke et al. (1972) reported that in 72 hours most of the radioactivity (65.5%) was excreted in the urine, 20.3% was excreted in the feces, and less than 0.1% appeared as carbon dioxide in expired air. About 85 to 95% of the urinary radioactivity appeared within the first 24 hours after dosing, indicating rapid clearance.

- Dauterman and Muecke (1974) have reported that atrazine metabolites are conjugated with glutathione to yield a mercapturic acid in the urine. The studies of Foster et al. (1979) in chicken liver homogenates also indicate that atrazine metabolism involves glutathione.

- Ciba-Geigy (1983b) studied the excretion rate of ^{14}C-atrazine from Harlan Sprague-Dawley rats dermally dosed with atrazine dissolved in tetrahydrofuran at levels of 0.025, 0.25, 2.5 or 5 mg/kg. Urine and feces were collected from all animals at 24-hour intervals for 144 hours. Results indicated that atrazine was readily absorbed, and within 48 hours most of the absorbed dose was excreted, mainly in the urine and to a lesser extent in the feces. Cumulative excretion in urine and feces appeared to be directly proportional to the administered dose, ranging from 52% at the lowest dose to 80% at the highest dose.

C. Health Effects

Humans

Short-Term Exposure

- A case of severe contact dermatitis was reported by Schlicher and Beat (1972) in a 40-year-old farm worker exposed to atrazine formulation. The clinical signs were red, swollen and blistered hands with hemorrhagic bullae between the

fingers. Although it is noted that the exposure of this patient may have been inclusive to exposure to other chemicals in addition to atrazine, it is also noted that atrazine is a skin irritant in animal studies.

Long-Term Exposure

- Yoder et al. (1973) examined chromosomes in lymphocyte cultures taken from agricultural workers exposed to herbicides including atrazine. There were more chromosomal aberrations in the workers during mid-season exposure to herbicides than during the off-season (no spraying). These aberrations included a four-fold increase in chromatid gaps and a 25-fold increase in chromatid breaks. During the off-season, the mean number of gaps and breaks was lower in this group than in controls who were in occupations unlikely to involve herbicide exposure. This observation led the authors to speculate that there is enhanced chromosomal repair during this period of time resulting in compensatory protection. However, these data may not be representative of the effect of atrazine since the exposed workers were also exposed to other herbicides.

Animals

Short-Term Exposure

- Acute oral LD_{50} values of 3,000 mg/kg in rats and 1,750 mg/kg in mice have been reported for technical atrazine by Bashmurin (1974); the purity of the test compound was not specified.

- Acute oral studies conducted by Ciba-Geigy (1988) with atrazine (97% a.i.) reflected the following LD_{50}s: 1,869 mg/kg in rats and >3,000 mg/kg in mice.

- Molnar (1971) reported that when atrazine was administered by gavage to rats at 3,000 mg/kg, 6% of the rats died within 6 hours, and 25% of those remaining died within 24 hours. The rats that died during the first day exhibited pulmonary edema with extensive hemorrhagic foci, cardiac dilation and microscopic hemorrhages in the liver and spleen. Rats that died during the second day had hemorrhagic bronchopneumonia and dystrophic changes of the renal tubular mucosa. Rats sacrificed after 24 hours had cerebral edema and histochemical alterations in the lungs, liver and brain. It is noted that the dose used in this study was almost 2 x the LD_{50} (Ciba-Geigy, 1988).

- Gaines and Linder (1986) determined the oral LD_{50} for adult male and female rats to be 737 and 672 mg/kg respectively and 2,310 mg/kg for pups. It is, therefore, noted that young animals are more sensitive to atrazine than adults. This study also reflected that the dermal LD_{50} for adult rats was higher than 2,500 mg/kg.

- Palmer and Radeleff (1964) administered atrazine as a fluid dilution or in gelatin capsules to Delaine sheep and dairy cattle (one animal per dosage group). Two doses of 250 mg/kg atrazine caused death in both sheep and cattle. Sixteen doses of 100 mg/kg were lethal to the one sheep tested. At necropsy, degeneration and discoloration of the adrenal glands and congestion in lungs, liver and kidneys were observed.

- Palmer and Radeleff (1969) orally administered atrazine 80W (analysis of test material not provided) by capsule or by drench to sheep at 5, 10, 25, 50, 100, 250, or 400 mg/kg/day and to cows at 10, 25, 50, 100, or 250 mg/kg/day. The number of animals in each dosage group was not stated, and the use of controls was not indicated. Observed effects included muscular spasms, stilted gait and stance, and anorexia at all dose levels in sheep and at 25 mg/kg in cattle. Necropsy revealed epicardial petechiae (small hemorrhagic spots on the lining of the heart) and congestion of the kidneys, liver and lungs. Effects appeared to be dose related. A Lowest-Observed-Adverse-Effect level (LOAEL) of 5 mg/kg/day in sheep and a No-Observed-Adverse-Effect level (NOAEL) of 10 mg/kg/day in cows can be identified from this study.

- Bashmurin (1974) reported that oral administration of 100 mg/kg of atrazine to cats had a hypotensive effect, and that a similar dose in dogs was antidiuretic and decreased serum cholinesterase (ChE) activity. No other details of this study were reported. Atrazine is not an organophosphate (OP); therefore, its effect on ChE may not be similar to the mechanism of ChE inhibition by OPs.

Dermal/Ocular Effects

- In a primary dermal irritation test in rats, atrazine at 2,800 mg/kg produced erythema but no systemic effects (Gzheyotskiy et al., 1977).

- Ciba-Geigy (1988) indicated that its studies reflected dermal sensitization in rats but not irritation in rabbits' eyes.

Long-Term Exposure

- Hazelton Laboratories (1961) fed atrazine to male and female rats for 2 years at dietary levels of 0, 1, 10, or 100 ppm. Based on the dietary assumptions of Lehman (1959), these levels correspond to doses of approximately 0, 0.05, 0.50, or 5.0 mg/kg/day. After 65 weeks, the 1.0-ppm dose was increased to 1,000 ppm (50 mg/kg/day) for the remainder of the study. No treatment-related pathology was found at 26 weeks, at 52 weeks, at 2 years, or in animals

that died and were necropsied during the study. Results of blood and urine analyses were unremarkable. Atrazine had no effects on the general appearance or behavior of the rats. A transient roughness of the coat and piloerection were observed in some animals after 20 weeks of treatment at the 10- and 100-ppm levels but not at 52 weeks. Body weight gains, food consumption, and survival were similar in all groups for 18 months, but from 18 to 24 months there was high mortality due to infections (not attributed to atrazine) in all groups, including controls, which limits the usefulness of this study in determining a NOAEL for the chronic toxicity of atrazine.

- In a 2-year study by Woodard Research Corporation (1964), atrazine (80W formulation) was fed to male and female beagle dogs for 105 weeks at dietary levels of 0, 15, 150, or 1,500 ppm. Based on the dietary assumptions of Lehman (1959), these levels correspond to doses of 0, 0.35, 3.5, or 35 mg/kg/day. Survival rates, body weight gain, food intake, behavior, appearance, hematologic findings, urinalyses, organ weights, and histologic changes wore noted. The 15- ppm dosage (0.35 mg/kg/day) produced no toxicity, but the 150-ppm dosage (3.5 mg/kg/day) caused a decrease in food intake as well as increased heart and liver weight in females. In the group receiving 1,500 ppm (35 mg/kg/day) atrazine, there were decreases in food intake and body weight gain, an increase in adrenal weight, a decrease in hematocrit and occasional tremors or stiffness in the rear limbs. There were no differences among the different groups in the histology of the organs studied. Based on these results, a NOAEL of 0.35 mg/kg/day can be identified for atrazine.

- In a study by Ciba-Geigy (1987b) using technical atrazine (97% ai.), 6-month-old beagle dogs were assigned randomly to four dosage groups: 0, 15, 150, and 1,000 ppm. These doses correspond to actual average intake of 0, 0.48, 4.97 and 33.65 /33.8 (male/female) mg/kg/day. Six animals/sex/group were assigned to the control and high dose groups and four animals/sex/group were assigned to the low- and mid-dose groups. One mid-dose male, one high-dose male, and one high dose female had to be sacrificed moribund during the study period. Decreased body weight gains and food consumption were noted at the high-dose level. Statistically significant ($p < 0.05$) reductions in erythroid parameters (red cell count, hemoglobin and hematocrit) in high-dose males were noted throughout the study, as well as mild increases in platelet counts in both sexes. Slight decreases in total protein and albumin ($p < 0.05$)were noted in high-dose males as well as decreased calcium and chloride in males and increased sodium and glucose in females. Decreases in absolute heart weight were noted in females and increased relative liver weight in males of the high-dose group. The mid-dose females reflected an increase in the absolute heart weight and heart/brain weight ratios. The most significant effect of atrazine in this study was reflected in the high-dose animals of both sexes as discrete myocardial degeneration. Clinical signs associated with cardiac pathology such as ascites, cachexia, labored/shallow breathing and abnormal EKG were observed in the group as early as 17 weeks into the study. Gross pathology reflected severe dilation of the right atrium and occasionally of the left atrium. These findings were also noted histopatho-logically as degenerative atrial myocardium (atrophy and myolysis). In the mid-dose group, two males and one female appeared to be affected with the cardiac syndrome but to a much lesser degree in the intensity of the noted responses. Therefore, the LOAEL in this study is 4.97 mg/kg/day and the NOAEL is 0.48 mg/kg/day.

- A 2-year chronic feeding/oncogenicity study (Ciba-Geigy, 1986) was recently evaluated by the Agency. In this study, technical atrazine (98.9% a.i.) was fed to 37-to 38-day-old Sprague-Dawley rats. The dosage levels used were 0, 10, 70, 500, or 1,000 ppm, equivalent to 0, 0.5, 3.5, 25, or 50 mg/kg/day (using Lehman's conversion factor, 1959). Twenty rats per sex per group were used to measure blood parameters and clinical chemistries and urinalysis. Fifty rats per sex per group were maintained on the treated and control diets for 24 months. An additional 10 rats per sex were placed on control and high dose (1,000 ppm) diets for a 12-month interim sacrifice and another 10 per sex (control and high dose, 1,000 ppm) for a 13-month sacrifice (the 1,000 ppm group was placed on control diet for 1 month prior to sacrifice). The total number of animals/sex in the control and HDT groups was 90 and 70 for the 10, 70, and 500 ppm groups. Histopathology was performed on all animals. At the mid- and high-dose, there was a decrease in mean body weights of males and females. Survival was decreased in high-dose females but increased in high-dose males. There were decreases in organ-to-body weight ratios in high-dose animals, which were probably the result of body weight decreases. Hyperplastic changes in high-dose males (mammary gland, bladder and prostate) and females (myeloid tissue of bone marrow and transitional epithelium of the kidney) were of questionable toxicologic importance. There was an increase in retinal degeneration and in centrolobular necrosis of the liver in high-dose females and an in-crease in degeneration of the rectus femoris muscle in high-dose males and females when compared to controls. Based on decreased body weight gain, the LOAEL for nononcogenic activities in both sexes is 25 mg/kg/day and the NOAEL is 3.5 mg/kg/day.

However, oncogenic activities were noted at 3.5 mg/kg/day (70 ppm) and above as reflected in the increased incidence of mammary gland tumors in females.

- A 91-week oral feeding/oncogenicity study in mice by Ciba-Geigy (1987c) has been evaluated by the Agency. In this study, atrazine (97% a, i.) was fed to 5-week-old CD-1 strain of mice, weighing 21.0/26.8 grams (female/male). The mice were randomly assigned to five experimental groups of approximately 60 animals/sex/ group. The dosage tested were 0, 10, 300, 1,500, and 3,000 ppm; these dosages correspond to actual mean daily intake of 1.4, 38.4, 194.0, and 385.7 mg/kg/day for males, and 1.6, 47.9, 246.9, and 482.7 mg/kg/day for females. This study shows that there are dose-related effects at 1,500 ppm or 3,000 ppm atrazine: an increase in cardiac thrombi, a decrease in the mean body weight gain at 12 and 91 weeks during the study, and decreases in erythrocyte count, hematocrit and hemoglobin concentration. Cardiac thrombi contributed to the deaths of the group of mice that did not survive to terminal sacrifice. The LOAEL is set at 1,500-ppm based upon decreases of 23.5% and 11.0% in mean body weight gain found at 91 weeks in male and female mice, respectively. Also, an increase in the incidence of cardiac thrombi is found in female mice in the 1,500 ppm exposure group. None of the above effects are found at 300 ppm; thus, the NOAEL is set at 300 ppm (corresponding to 38.4 mg/kg/day in males and 47.9 mg/kg/day for females).

Reproductive Effects

- A three-generation study on the effects of atrazine on reproduction in rats was conducted by Woodard Research Corporation (1966). Groups of 10 males and 20 females received atrazine (SOW) at dietary levels of 0, 50, or 100 ppm. Based on the dietary assumption that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of approximately 0, 2.5, or 5 mg/kg/day. Two litters were produced per generation, but parental animals were chosen from the second litter after weaning for each generation. Young rats were maintained on the test diets for approximately 10 weeks in each generation. The third-generation pups were sacrificed after weaning. It is noted that the parental animals of the first generation were fed only half of the dietary atrazine levels for the first 3 weeks of exposure. There were no adverse effects of atrazine on reproduction observed during the course of the three-generation study. A NOAEL of 100 ppm (5 mg/kg/day) was identified from this study. However, the usefulness of this study is limited due to the alteration of the atrazine content of the diet during important maturation periods of the neonates.

- A recent two-generation study in rats by Ciba-Geigy (1987a) was conducted using the 97% a.i. technical atrazine. Young rats, 47 to 48 days old, were maintained on the control and test diets for 10 weeks before mating. The concentrations used were 0, 10, 50, and 500 ppm (equivalent to 0, 0.5, 2.5, and 25 mg/kg/day using Lehman conversion factor, 1959). Thirty animals/sex/group were used in each generation; one litter was produced per generation. The level tested had no effect on mortality in either generation. Body weight and body weight gains were significantly depressed ($p<0.05$) at the highest dose; however, food consumption was also decreased at this high-dose level in parental males and females during the premating period and for the first generation females (F_1) on days 0 to 7 of gestation. Neither histopathological nor other effects were noted during gross necropsy in either parental generation, with the exception of increased relative weight of testes in both generations at the high dose. In pups of both generation, significant reduction ($p<0.05$) in body weight was noted; however, this effect was only dose-related in the second generation (F_2) at both the mid- and high-dose levels on postnatal day 21. Therefore, maternal toxicity NOAEL is 2.5 mg/kg/day; the reproductive LOAEL is 2.5 mg/kg/day (reduced pup weight in F_2 generation on postnatal day 21), and the NOAEL is 0.5 mg/kg/day.

Developmental Effects

- In the three-generation reproduction study in rats conducted by Woodard Research Corporation (1966) (described above), atrazine at dietary levels of 50 or 100 ppm (2.5 or 5 mg/kg/day) resulted in no observed histologic changes in the weanlings and no effects on fetal resorption. No malformations were observed, and weanling organ weights were similar in controls and atrazine-treated animals. Therefore, a NOAEL of 100 ppm (5 mg/kg/day) was also identified for developmental effects in this study. However, the usefulness of this study is limited due to an alteration of the atrazine content of the diet during important maturation periods of the neonates.

- Atrazine was administered orally to pregnant rats on gestation days 6 to 15 at 0, 100, 500 or 1,000 mg/kg (Ciba-Geigy, 1971). The two higher doses increased the number of embryonic and fetal deaths, decreased the mean weights of the fetuses and retarded the skeletal development. No teratogenic effects were observed. The highest dose (1,000 mg/kg) resulted in 23% maternal mortality and various toxic symptoms. The 100 mg/kg dose had no effect on either dams or embryos and is therefore the maternal and fetotoxic NOAEL in this study.

- In a study by Ciba-Geigy (1984a), Charles River rats received atrazine (97%) by gavage on gestation days 6 to 15 at dose levels of 0, 10, 70, or 700 mg/kg/day. Excessive maternal mortality (21/27) was noted at 700 mg/kg/day, but no mortality was noted at the lower doses; also, reduced weight gains and food consumption were noted at both 70 and 700 mg/kg/day. Developmental toxicity was also present at these dose levels. Fetal weights were severely reduced at 700 mg/kg/day; delays in skeletal development occurred at 70 mg/kg/ day, and a dose-related runting was noted at 10 mg/kg/day and above. The NOAEL for maternal toxicity appears to be 10 mg/kg/day; however, this is also the LOAEL for developmental effects.

- New Zealand white rabbits received atrazine (96%) by gavage on gestation days 7 through 19 at dose levels of 0, 1, 5, or 75 mg/kg/day (Ciba-Geigy, 1984b). Maternal toxicity, evidenced by decreased body weight gains and food consumption, was present in the mid- and high-dose groups. Developmental toxicity was demonstrated only at 75 mg/kg/day by an increased resorption rate, reduced fetal weights, and delays in ossification. No teratogenic effects were indicated. The NOAEL appears to be 1 mg/kg/day.

- Peters and Cook (1973) fed atrazine to pregnant rats (four/group) at levels of 0, 50, 100, 200, 300, 400, 500, or 1,000 ppm in the diet throughout gestation. Based on an assumed body weight of 300 g and a daily food consumption of 12 g (Arrington, 1972), these levels correspond to approximately 0, 2, 4, 8, 12, 16, 20, or 40 mg/kg/day. The number of pups per litter was similar in all groups, and there were no differences in weanling weights. This study identified a NOAEL of 40 mg/kg/day for developmental effects. In another phase of this study, the authors demonstrated that subcutaneous (sc) injections of 50, 100, or 200 mg/kg of atrazine on gestation days 3, 6 and 9 had no effect on the litter size, while doses of $\geq$800 mg/kg were embryotoxic. Therefore, a NOAEL of 200 mg/kg by the sc route was identified for embryotoxicity.

Mutagenicity

- Loprieno et al. (1980) reported that single doses of atrazine (1,000 mg/kg or 2,000 mg/kg, route not specified) produced bone marrow chromsomal aberrations in the mouse. No other details of this study were provided.

- Murnik and Nash (1977) reported that feeding 0.01% atrazine to male *Drosophila melanogaster* larvae significantly increased the rate of both dominant and sex-linked recessive lethal mutations. They stated, however, that dominant lethal induction and genetic damage may not be directly related.

- Adler (1980) reviewed unpublished work on atrazine mutagenicity carried out by the Environmental Research Programme of the Commission of the European Communities. Mutagenic activity was not induced even when mammalian liver enzymes (5-9) were used; however, the use of plant microsomes produced positive results. Also, *in vivo* studies in mice, atrazine induced dominant lethal mutations and increased the frequency of chromatid breaks in bone marrow. Hence, the author suggested that activation of atrazine in mammals occurs independently of the liver, possibly in the acidic part of the stomach.

- As described previously, Yoder et al. (1973) studied chromosomal aberrations in the lymphocyte cultures of farm workers exposed to various pesticides including atrazine. During mid-season a 4-fold increase in chromatid gaps and a 25-fold increase in chromatid breaks was observed. During the off-season (no spraying), the number of gaps and breaks was lower than in controls, suggesting that chromosomal repair is enhanced during the unexposed period.

- Recently, Spencer (1987) and Dearfield (1988) evaluated several *in vitro* and *in vivo* mutagenicity studies on atrazine that were recently submitted to the U.S. EPA by Ciba-Geigy. They noted that most of these studies were inadequate with the exception of the following three tests: a *Salmonella* assay; an *E. coli* reversion assay, and a host-mediated assay. The first two assays were negative for mutagenic effects; the results of the third assay were equivocal.

- Ciba-Geigy (1988) indicated that Brusick (1987) evaluated atrazine mutagenicity and that the weight-of-evidence analysis he used placed the chemical in a nonmutagenic status. The Agency (Dearfield, 1988) evaluated Brusick's analysisand determined that using the weight-of-evidence approach is not appropriate at the present time. The *in vivo* studies by Adler (1980) suggest a positive response. These findings have not been diminished by other atrazine studies. In addition, Dearfield (1988) indicated that the scheme used by Brusick in this analysis is flawed by the lack of calibration of the chemical test scores to an external standard and by the use of some studies that are considered inadequate by design to determine the mutagenic potential of atrazine.

Carcinogenicity

- Innes et al. (1969) investigated the tumorigenicity of 120 test compounds, including atrazine, in mice.

Two F_1 hybrid stocks (C57BL/6 x Anf) F_1 and (C57BL/6 x AKR) F_1 were used. A dose of 21.5 mg/kg/day was administered by gavage to mice of both sexes from age 7 to 28 days. After weaning at 4 weeks, this dose level was maintained by feeding 82 ppm atrazine *ad libitum* in the diet for 18 months. The incidence of hepatomas, pulmonary tumors, lymphomas and total tumors in atrazine-treated mice was not significantly different from that in the negative controls.

- A 2-year feeding/oncogenicity study in rats by Ciba-Geigy (1986) has been evaluated recently by the Agency. Atrazine (98.9% a.i.) was fed to 37-to 38-day-old Sprague-Dawley rats. The dosage levels used were 0, 10, 70, 500, or 1,000 ppm, equivalent to 0, 0.5, 3.5, 25, or 50 mg/kg/day (using Lehman's conversion factor, 1959). The total number of animals/sex in the control and HDT groups was 90; and 70 animals/sex/group for the 10, 70 and 500 ppm groups. Histopathology was performed on all animals. In females, atrazine was associated with a statistically significant increase in mammary gland fibroadenomas at 1,000 ppm; in mammary gland adenocarcinomas (including two carcinosarcomas at the HDT) at 70, 500, and 1,000 ppm, and in total mammary gland tumor bearing animals at 1,000 ppm. Each of these increases was associated with a statistically significant dose-related trend and was outside of the high end of the historical control range. In addition, EPA (1986a) indicated that there was evidence for decreased latency for mammary gland adenocarcinomas at the 12- month interim sacrifice that was already submitted by Ciba-Geigy in 1985. This study was also reported as positive in a briefing paper by Ciba-Geigy (1987).

- A recent 91-week oral feeding/oncogenicity study in mice by Ciba-Geigy (1987c) has been evaluated by the Agency. In this study, atrazine (97% a. i.) was fed to 5-week-old CD-1 mice weighing 21.0/26.8 g (female/male). The mice were randomly assigned to five experimental groups of approximately 60 animals/sex/ group. The dosage tested were 0, 10, 300, 1,500, and 3,000 ppm: these dosages correspond to actual mean daily intake of 1.4, 38.4, 194.0, and 385.7 mg/kg/day for males, and 1.6, 47.9, 246.9, and 482.7 mg/kg/day for females. The following kinds of neoplasms were noted in this study: mammary adenocarcinomas, adrenal adenomas, pulmonary adenomas, and malignant lymphomas. However, no dose-related or statistically significant increases were observed in the incidences of these neoplasms. Therefore, atrazine is not considered oncogenic in this strain of mice.

D. Quantification of Toxicological Effects

The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (BW)}{(UF) \times (\_\_\ \text{L/day})}$$

$$= \_\_\_\_\_ \text{mg/L (ug/L)}$$

where:

NOAEL or LOAEL	=	No- or Lowest-Observed-Adverse-Effect level in mg/kg bw/day.
BW	=	assumed body weight of a child (10 kg) or an adult (70 kg).
UF	=	uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW
__L/day	=	assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-Day Health Advisory

No suitable information was found in the available literature for the determination of the One-Day HA value for atrazine. It is, therefore, recommended that the Ten-Day HA value calculated below for a 10-kg child of 0.1 mg/L (100 µg/L), be used at this time as a conservative estimate of the One-Day HA value.

Ten-Day Health Advisory

Two teratology studies by Ciba-Geigy, one in the rat (1984a) and one in the rabbit (1984b), were considered for the calculation of the Ten-Day HA value. The rat study reflected a NOAEL of 10 mg/kg/day for maternal toxicity, but this value was also the LOAEL for developmental toxicity. The rabbit study reflected a NOAEL of 5 mg/kg/day for developmental toxicity and 1 mg/kg/day for maternal toxicity. Thus, the rabbit appears to be a more sensitive species than the rat for maternal toxicity. Hence, the rabbit study with a NOAEL of 1 mg/kg/day is used in the calculations below.

The Ten-Day HA for a 10-kg child is calculated below as follows:

$$\frac{(1\ mg/kg/d) \times (10\ kg)}{(100) \times (1\ L/day)} = 0.1\ mgL\ (100\ ug/L)$$

where:

1 mg/kg/day	=	NOAEL, based on maternal toxicity evidenced by decreased body weight gain and food consumption.

10 kg	=	assumed body weight of a child.
100	=	uncertainty factor, chosen in accordance with EPA or ODW/NAS guidelines for use with a NOAEL from an animal study.
1 L/day	=	assumed daily consumption for a child.

Longer-Term Health Advisory

No suitable information was found in the available literature for the determination of the Longer-Term HA value for atrazine. It is, therefore, recommended that the adjusted DWEL for a 10-kg child of 0.05 mg/L (50 µg/L) and the DWEL for a 70-kg adult of 0.2 mg/L (200 µg/L) be used at this time as conservative estimates of the Longer-Term HA value.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor (s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986b), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Three studies were considered for the development of the Lifetime HA. A 2-year dog feeding study (Woodard, 1964), a 1-year dog feeding study Ciba-Geigy, 1987b) and a 2-year rat oral feeding/oncogenicity study (Ciba-Geigy, 1986).

The first study in dogs (1964) reflected a NOAEL of 0.35 mg/kg/day and a LOAEL of 3.5 mg/kg/day that was associated with increased heart and liver weights in females. The new 1 year dog study (1988) reflected a NOAEL of 0.48 mg/kg/day and a LOAEL of 4.97 mg/kg/day based on mild cardiac pathology intensified at the higher dose tested 33.65/33.8 (male/female) mg/kg/day. The 2 year rat study (Ciba-Geigy, 1986) reflected a NOAEL at 3.5 mg/kg/day for systemic effects other than oncogenicity; however, this study indicated hat atrazine caused mammary gland tumors at this dose level and above, no adverse effects were observed at the lowest dose tested, 0.5 mg/kg/day.

The 1964 dog study was initially used for the calculation of the RfD and the Lifetime HA. However, this study was partially flawed by the lack of information on the purity of the test material and by the inadequate documentation of the hematological data. Therefore, the recent 1-year dog study (Ciba-Geigy, 1987b), using technical atrazine (97% a. i.), is considered a more adequate study for the calculation of the RfD and the Lifetime HA. The NOAEL in this study, 0.48 mg/kg/day, is also supported by the NOAEL of 0.5 mg/kg/day in the 2 generation reproduction study (Ciba-Geigy, 1987a) and by the fact that no systemic effects or tumors were noted at this dose level in the two-year chronic feeding/oncogenicity study in rats (Ciba-Geigy, 1986). [Other studies: Woodard Research Corporation (1966) and Hazelton Laboratories (1961) identified long-term NOAEL values of 5 to 50 mg/kg/day and were not considered to be as protective as the dog studies for use in calculating the HA values for atrazine.]

Step 1: Determination of the RfD

$$RfD = \frac{0.48\ mg/kg/day}{(100)} = 0.005\ mg/hg/day$$

(rounded from 0.0048 mg/kg/day)

where:

0.48 mg /kg/day	=	NOAEL, based on the absence of cardiac pathology or any other/adverse clinical, hematological, biochemical and histopathological effects in dogs.
100	=	uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the DWEL

$$DWEL = \frac{0.0048\ mg/kg/day\ (70-kg)}{(2\ L/day)}$$

$$= 0.168\ mg/L\ (200 ug/L)$$

where:

0.0048 mg /kg/day	=	RfD (before rounding off to 0.005 mg/kg/day).
70 kg	=	assumed body weight of an adult.
2 L/day	=	assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (0.168 mg/L)(20%)/10
= 0.003 mg/L (3 µg/L)

where:

0.168 mg/L	=	DWEL (before rounding off to 0.2 mg/L)
20%	=	assumed relative source contribution from water.
10	=	additional uncertainty factor, according to ODW policy, to account for possible carcinogenicity.

Evaluation of Carcinogenic Potential

- A study submitted by Ciba-Geigy Corporation (1986) in support of the pesticide registration of atrazine indicated that atrazine induced an increased incidence of mammary tumors in female Sprague-Dawley rats. These findings have been further confirmed in a briefing by Ciba-Geigy (1987) on this study.

- Atrazine was not oncogenic in mice (Ciba-Geigy, 1987c).

- Three closely related analogs – propazine, terbutryn and simazine – are presently classified as Group C oncogens based on an increased incidence of tumors in the same target tissue (mammary gland) and animal species (rat) as was noted for atrazine

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of atrazine.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986b), atrazine may be classified in Group C: possible human carcinogen. This category is used for substances with limited evidence of carcinogenicity in animals in the absence of human data.

E. Other Criteria, Guidance, and Standards

- Toxicity data on atrazine were reviewed by the National Academy of Sciences (NAS, 1977), and the study by Innes et al. (1969) was used to identify a chronic NOAEL of 21.5 mg/kg/day. Although at that time it was concluded that atrazine has low chronic toxicity, an uncertainty factor of 1,000 was employed in calculation of the ADI from that study, since only limited data were available. The resulting value (0.021 mg/kg/day) corresponds to an ADI of 0.73 mg/L in a 70-kg adult consuming 2 L of water per day.

- Tolerances for atrazine alone and the combined residues of atrazine and its metabolites in or on various raw agricultural commodities have been established (U.S. EPA, 1986c). These tolerances range from 0.02 ppm (negligible) in animal products (meat and meat by-products) to 15 ppm in various animal fodders.

F. Analytical Methods

- Analysis of atrazine is by a gas chromatographic (GC) method, Method No. 507, applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1988). In this method, approximately 1 L of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column CC. Measurement is made using a nitrogen phosphorus detector. The method has been validated in a single laboratory. The estimated detection limit for the analytes in this method, including atrazine, is 0.13 µg/L.

G. Treatment Technologies

- Treatment technologies that remove atrazine from water include activated carbon adsorption, ion exchange, reverse osmosis, ozone oxidation, and ultraviolet irradiation. Conventional treatment methods are ineffective for the removal of atrazine from drinking water (ESE, 1984; Miltner and Fronk, 1985a). Limited data suggest that aeration would not be effective in atrazine removal (ESE, 1984; Miltner and Fronk, 1985a).

- Baker (1983) reported that a 16.5-inch GAC filter cap using F-300, which was placed on the rapid sand filters at the Fremont, Ohio water treat-ment plant, reduced atrazine levels by 30 to 64% in the water from the Sandusky River. At Jefferson

Parish, Louisiana, Lykins et al. (1984) reported that an adsorber containing 30 inches of Westvaco WV-G 12 x 40 GAC removed atrazine to levels below detectable limits for over 190 days.

- At the Bowling Green, Ohio, water treatment plant, PAC in combination with conventional treatment achieved an average reduction of 41% of the atrazine in the water from the Maumee River (Baker, 1983). Miltner and Fronk (1985a) reported that in jar tests using spiked Ohio River water with the addition of 16.7 and 33.3 mg/L of PAC and 15-20 mg/L of alum, PAC removed 64 and 84%, respectively, of the atrazine. Higher percent removals reflected higher PAC dosages. Miltner and Fronk (1985b) monitored atrazine levels at water treatment plants, which utilized PAC, in Bowling Green and Tiffin, Ohio. Applied at dosages ranging from 3.6 to 33 mg/L, the PAC achieved 31 to 91% removal of atrazine, with higher percent removals again reflecting higher PAC dosages.

- Harris and Warren (1964) reported that Amberlite IR-120 cation exchange resin removed atrazine from aqueous solution to less than detectable levels. Turner and Adams (1968) studied the effect of varying pH on different cation and anion exchange resins. At a pH of 7.2, 45% removal of atrazine was achieved with Dowex® 2 anion exchange resin and with H2P04-as the exchangeable ion species.

- Chian et al. (1975) reported that reverse osmosis, utilizing cellulose acetate membrane and a cross-linked polyethelenimine (NS-100) membrane, successfully processed 40% of the test solution, removing 84 and 98%, respectively, of the atrazine in the solution.

- Miltner and Fronk (1985a) studied the oxidation of atrazine with ozone in both spiked distilled and ground water. Varying doses of ozone achieved a 70% removal of atrazine in distilled water and 49 to 76% removal of atrazine in ground water.

- Kahn et al. (1978) studied the effect of fulvic acid upon the photo-chemical stability of atrazine to ultraviolet irradiation. A 50% removal of atrazine was achieved much faster at higher pH conditions than at lower pH conditions. In the presence of fulvic acids, the time needed for ultraviolet irradiation to achieve 50% removal was almost triple the time required to achieve similar removals without the presence of fulvic acids. Since fulvic acids will be present in surface waters, ultraviolet irradiation may not be a cost-effective treatment alternative.

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IV. TRICHLOROETHYLENE

A General Information and Properties

CAS No.: 79-01-6

Structural Formula: $Cl\text{-}HC{=}C\text{-}Cl_2$

Trichloroethylene

Synonyms:

TCE, trichloroethene, acetylene trichloride, Tri, Trilene

Uses:

Industrial solvent and degreaser for metal components

Properties: (Torkelson and Rowe, 1981; Windholtz, 1983)

Chemical formula	C_2HCl_3
Molecular weight	131.40
Physical state	Colorless liquid
Boiling point	86.7°C
Vapor pressure	77 mm (25°C)
Density at 25°C	1.4 g/mL
Water solubility	0.1 g/100 mL (20°C)
Odor threshold (water)	0.5 mg/L
Odor threshold (air)	2.5-900 mg/m^3
Organoleptic threshold (water)	0.31 mg/L (Amoore and Hautala, 1983)
Conversion factor	1 ppm = 5.46 mg/m^3

Occurrence

- Trichloroethylene (TCE) is a synthetic chemical with no natural sources.
- Production of TCE was 200 million lb in 1982 (U.S. ITC, 1983).
- The major source of TCE released to the environment is its use as a metal degreaser. Since TCE is not consumed during this use, the majority of all TCE production is released to the environment. Most of the releases occur to the atmosphere by evaporation. However, TCE that is not lost to evaporation becomes heavily contaminated with grease and oil and has been disposed of by burial in landfills, dumping on the ground, or into sewers. Because metal working operations are performed nationwide, TCE releases occur in all industrialized areas. Releases of TCE during production and other uses are relatively minor.
- Trichloroethylene released to the air is degraded in a matter of a few days. Trichloroethylene released to surface waters migrates to the atmosphere in a few days or weeks, where it also degrades. Photo-oxidation appears to be the predominant fate of this compound (U.S. EPA, 1979). Trichloroethylene released to the land does not degrade rapidly, migrates readily to ground water and remains in ground water for months to years. Under certain conditions, TCE in ground water appears to degrade to dichloro-ethylene and vinyl chloride. Trichloroethylene also may be formed in ground water by the degra-dation of tetrachloroethylene TCE, unlike other chlorinated

compounds, does not bioaccumulate in individual animals or food chains.

- Because of the large and dispersed releases, TCE occurs widely in the environment. Trichloroethylene is ubiquitous in the air, with levels in the ppt to ppb range. Trichloroethylene is a common, contaminant in ground and surface waters awith higher levels found in ground water. Surveys of drinking water supplies have found that 3% of all public systems derived from well water contain TCE at levels of 0.5 µg/L or higher. A small number of systems (0.04%) have levels higher than 100 µg/L. Public systems derived from surface water also have been found to contain TCE but at lower levels. Trichloro-ethylene has been reported to occur in some foods in the ppm range.

B. Pharmacokinetics

Absorption

- Data on absorption of ingested TCE are limited. When a dose of 200 mg/kg of ^{14}C-TCE in corn oil was administered to rats, 97% of the dose was recovered during 72 hours after dosing (De Kant et al., 1984).

Distribution

- Doses of 0, 10, 100, or 1,000 mg TCE/kg/day were administered by gavage to rats 5 days/week for 6 weeks (Zenick et al., 1984). Marginal increases in TCE tissue levels were detected in the 10 mg/kg/day and 100 mg/kg/day dose groups. Compared to controls, a marked increase in TCE levels in most tissues was observed in the highest dose group. Trichloroethylene was distributed in all tissues examined with the highest concentrations in the fat, kidney, lung, adrenals, vas deferens, epididymis, brain, and liver.

Metabolism

- Studies indicate that TCE is metabolized to trichloroethylene oxide, trichloracetaldehyde, trichloroacetic acid, monochloroacetic acid, trichloroethanol, and trichloroethanol glucuronide (EPA, 1985a).

Excretion

- Trichloroethylene and its metabolites are excreted in urine, by exhalation and, to a lesser degree, in sweat, feces, and saliva (Soucek and Vlachova, 1959).

C. Health Effects

Humans

Short-term Exposure

- Oral exposure of humans to 15 to 25 mL (21 to 35 g) quantities of TCE resulted in vomiting and abdominal pain, followed by transient unconsciousness (Stephans, 1945).

Long-Term Exposure

- Studies of humans exposed occupationally have shown an increase in serum transaminases, which indicates damage to the liver parenchyma (Lachnit, 1971). Quantitative exposure levels were not available.

Animals

Short-Term Exposure

- The acute oral LD_{50} of TCE in rats is 4.92 g/kg (NIOSH, 1980).

Long-Term Exposure

- Rats exposed to 300 mg/m^3 (55 ppm) TCE 5 days/week for 14 weeks had elevated liver weights (Kimmerle and Eben, 1973).

Reproductive Effects

- No data were available on the reproductive effects of TCE.

Developmental Effects

- No data were available on the developmental effects of TCE.

Mutagenicity

- Trichloroethylene was mutagenic in *Salmonella typhimurium* and in the *E. coli* K-12 strain, utilizing liver microsomes for activation (Greim et al., 1975, 1977).

Carcinogenicity

- Technical TCE (containing epichlorohydrin and other compounds) was found to induce a hepatocellular carcinogenic response in B6C3F$_1$ mice (NCI, 1976). Under the conditions of this experiment, a carcinogenic response was not observed in Osborne-Mendel rats. The "time-weighted" average doses were 549 and 1,097 mg/kg for both male and female rats. The time-

weighted average daily doses were 1,169 and 2,339 mg/kg for male mice and 869 and 1,739 mg/kg for female mice.

- Epichlorohydrin-free TCE was reported to be carcinogenic in B6C3F$_1$ mice when administered in corn oil at 1,000 mg/kg/day, 5 days/wk, for 103 weeks (NTP, 1982). It was not found to be carcinogenic in female Fischer 344 rats when administered in corn oil at 500 or 1,000 mg/kg/day, 5 days/wk, for 103 weeks. The experiment with male rats was considered to be inadequate since these rats received doses of TCE that exceeded the maximum tolerated dose.

- TCE has been shown to be carcinogenic in mice utilizing the inhalation as well as the oral route of exposure. The National Cancer Institute (1976) and the National Toxicology Program (1982) each conducted an oral gavage study with TCE, one contaminated with epichlorohydrin and the other free of epichlorohydrin, respectively. In these studies, as described above, B6C3F$_1$ mice were used, and the results were unequivocally positive, showing liver neoplasms.

- In an inhalation study, Henschler et al. (1980) reported dose-related malignant lymphomas in female mice exposed to 100 or 500 ppm TCE vapor 6 hr/day, 5 days/wk, for 18 months (HAN:NMRI strain). However, the authors downplayed the significance of this observation, indicating that this strain of mice has a high incidence of spontaneous lymphomas.

- Fukuda et al. (1983) found pulmonary adenocarcinomas in female ICR mice on exposure to TCE vapor.

- Henschler et al. (1984) tested Swiss (ICR/HA) mice and reported that when the animals were treated by gavage with TCE in corn oil, no statistical differences were observed in the incidence of cancers. The results of this study can be questioned because the dose schedule was often interrupted even with half of the original dose. Therefore, it is very difficult to assess the exposure. A slight increase in tumors was found in all groups treated with TCE but did not approach statistical significance.

- The van Duuren study (1979) with skin applications of TCE in ICR/HA mice does not negate the positive findings with other strains of mice and other routes of exposure.

D. Quantification of Toxicological Effects

The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL\ or\ LOAEL) \times (BW)}{(UF) \times (\_\_\ L/day)}$$

$$= \_\_\_\_\_\ mg/L\ (\_\_\_\_\_\ \mu g/L)$$

where:

NOAEL or LOAEL	=	No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.
BW	=	assumed body weight of a child (10 kg) or an adult (70 kg).
UF	=	uncertainty factor (10, 100, or 1,000), in accordance with NAS/ODW guidelines.
____L/day	=	assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-Day and Ten-Day Health Advisory

Suitable data were not available to estimate One-Day and Ten-Day Health Advisories.

Longer-Term Health Advisory

No suitable data are available from which to calculate a Longer-Term Health Advisory.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The

RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the cotaminant is classified as a Group A or B crcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Trichloroethylene may be classified in Group B: Probable Human Carcinogen, according to EPA's weight-of-evidence scheme for the classification of carcinogenic potential (U.S. EPA, 1986). Because of this, caution must be exercised in making a decision on how to deal with possible lifetime exposure to this substance. The risk manager must balance this assessment of carcinogenic potential against the likelihood of occurrence of health effects related to noncarcinogenic end points of toxicity. In order to assist the risk manager in this process, drinking water concentrations associated with estimated excess lifetime cancer risks over the range of one in ten thousand to one in a million for the 70 kg adult, drinking 2 L of water per day, are provided in the following section. In addition, in this section, a DWEL is derived.

Neither the risk estimates nor the DWEL take RSC into account. The risk manager should do this on a case-by-case basis, considering the circumstances of the specific contamination incident that has occurred.

The study by Kimmerle and Eben (1973) is the most appropriate from which to derive the DWEL. This study evaluated the subacute exposure to trichloroethylene via inhalation by adult rats for some 14 weeks following exposure to 55 ppm (300 mg/m^3), 5 days a week. Indices of toxicity include hematological investigation, liver and renal function tests, blood glucose, and organ/ body weight ratios. Liver weights were shown to be elevated while other test values were not different from controls. The elevated liver weights could be interpreted to be the result of hydropic changes or fatty accumulation. The No-Observed-Effect level was not identified since only a single concentration was administered. From these results, a LOAEL of 55 ppm (300 mg/m^3) was identified. With the LOAEL, the DWEL is derived as follows:

Step 1: Determination of the Total Absorbed Dose (TAD)

$$TAD = \frac{(300\ mg/m^3)\,(8\ m^3/day)\,(5/7)\,(0.3)}{(70\ kg)}$$

$$= 7.35\ mg/kg/day$$

where:

300 mg/m^3	=	LOAEL for liver effects in rats.
8 m^3/day	=	volume of air inhaled during the exposure period.
5/7	=	conversion factor for adjusting from 5 days/week exposure to a daily dose
0.3	=	ratio of the dose absorbed.
70 kg	=	assumed weight of adult.

Step 2: Determination of the RfD

$$RFD = \frac{7.35\ mg/kg/day}{(100)\,(10)}$$

$$= 0.00735\ mg/kg/day$$

where:

7.35 mg/kg/day	=	TAD
1,000	=	uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

Step 3: Determination of the DWEL

$$DWEL = \frac{(0.00735\ mg/kg/day)\,(70\ kg)}{2\ L/day}$$

$$= 0.26\ mg/L\ (260\ \mu g/L)$$

where:

0.00735 mg /kg/day	=	RfD.
70 kg	=	assumed body weight of an adult.
2 L/day	=	assumed daily water consumption of an adult.

The estimated excess cancer risk associated with lifetime exposure to drinking water containing TCE at 260 µg/L is approximately 1 x 10^{-4}. This estimate represents the upper 95% confidence limit from extrapolations prepared by EPA's Carcinogen Assessment Group using the linearized, multistage model. The actual risk is unlikely to exceed this value, but there is considerable uncertainty as to the accuracy of risks calculated by this methodology.

Evaluation of Carcinogenic Potential

- IARC (1982) has classified TCE in Group 3.
- EPA has classified trichloroethylene in Group B2: Probable Human Carcinogen. This classification

for carcinogenicity was determined by a technical panel of EPA's Risk Assessment Forum using the EPA risk assessment guidelines for carcinogens (U.S. EPA, 1986). This category is used for agents for which there is "sufficient evidence" for human carcinogenicity from animal" studies and for which there is "inadequate evidence" or "no data" from human studies.

- With the improved multistage linearized model, estimates can be made that water with TCE concentrations of 280 µg/L, 28 µg/L, or 2.8 µg/L may increase the risk of one excess cancer per 10^4, 10^5, or 10^6 people exposed, respectively. These estimates were calculated from the 1976 NCI bioassay data, which utilized TCE contaminated with epichlorohydrin. Since then, an NTP (1982) bioassay utilizing epichloro-hydrin-free TCE has become available; the data from this bioassay have been reviewed and evaluated for carcinogenicity, and epichlorohydrin-free TCE has been reported to be carcinogenic in mice.

E. Other Criteria, Guidance, and Standards

- ACGIH (1984) has recommended a threshold limit value (TLV) of 50 ppm (~270 mg/m^3) and a short-term exposure limit (STEL) of 150 ppm (~805 mg/m^3).

- The NAS (1980) recommended One- and Seven-Day SNARLs of 105 and 15 mg/L, respectively.

- WHO (1981) recommended a drinking water guidance level of 30 µg/L based on a carcinogenic end point.

- The EPA (U.S. EPA, 1980) recommended a water quality criterion of 6.77 mg/L for effects other than cancer.

- The EPA (U.S. EPA, 1985d) has promulgated a Recommended Maximum Contaminant Level (RMCL) of zero based upon TCE's classification as a known or probable human carcinogen and has proposed a Maximum Contaminant Level (MCL) of 0.005 mg/L based on its RMCL and appropriate feasibility studies.

F. Analytical Methods

- Analysis of TCE is by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water (U.S. EPA, 1985b). This method calls for the bubbling of an inert gas through the sample and trapping TCE on an adsorbent material. The adsorbent material is heated to drive off the TCE onto a gas chromatographic column. This method is applicable to the measurement of TCE over a concentration range of 0.01 to 1500 µg/L. Confirmatory analysis for TCE is by mass spectrometry (U.S. EPA, 1985c). The detection limit for confirmation by mass spectrometry is 0.2 µg/L.

G. Treatment Technologies

- Treatment technologies that will remove TCE from water include granular activated carbon (GAC) adsorption, aeration and boiling.

- Dobbs and Cohen (1980) developed adsorption isotherms for several organic chemicals including TCE. Fibrasorb® 300 carbon exhibited adsorptive capacities of 7, 1.6, and 0.4 mg TCE/gm carbon at equilibrium concentrations of 100, 10, and 1 mg/L, respectively. USEPA-DWRD installed pilot-scale adsorption columns at different sites in New England and Pennsylvania. In New England, contaminated well water with TCE concentrations ranging from 0.4 to 177 mg/L was passed through GAC columns until a break-through concentration of 0.1 mg/L was achieved with empty bed contact time (EBCT) of 18 and 9 minutes, respectively (Love and Eilers, 1982). In Pennsylvania, TCE concentrations ranging from 20 to 130 mg/L were reduced to 4.5 mg/L by GAC after 2 months of continuous operation (ESE, 1985).

- TCE is amenable to aeration on the basis of its Henry's Law constant of 550 atm (Kavanaugh and Trussell, 1980). In a full plant-scale (3.78 MGD) redwood slat tray aeration column, a removal efficiency of 50-60% was achieved from TCE initial concentrations of 8.3-39.5 mg/L at an air-to-water ratio of 30:1 (Hess et al., 1981). In another full plant-scale (6.0 MGD) multiple tray aeration column study, TCE removal of 52% was achieved from 150 mg/L (Hess at al., 1981). A full plant-scale packed tower aeration column removed 97-99% of TCE from 1,500-2,000 mg/L contaminated groundwater at air-to-water ratio of 25:1 (ESE, 1985).

- Boiling also is effective in eliminating TCE from water on a short-term, emergency basis. Studies have shown 5 minutes of vigorous boiling will remove 95% of TCE originally present (Love and Ellers, 1982).

- Air stripping is an effective, simple, and relatively inexpensive process for removing TCE and other volatile organics from water. However, use of this process then transfers the contam-inant directly to the air stream. When consider-ing use of air stripping as a treatment process, plant managers must factor in the overall environmental occurrence, fate, route of ex-posure, and various other hazards associated with the chemical.

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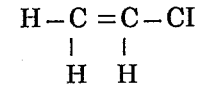
V. VINYL CHLORIDE

A. General Information and Properties

CAS No.: 75-01-4

Structural Formula:



Synonyms:

- Monochloroethylene, chloroethene

Uses:

- Vinyl chloride and polyvinyl chloride (PVC) are used as raw materials in the plastics, rubber, paper, glass and automotive industries. In addition, vinyl chloride and PVC are used in the manufacture of electrical wire insulation and cables, piping, industrial and household equipment, medical supplies, food packaging materials and building and construction products. Vinyl chloride copolymers and PVC are distributed and processed in a variety of forms, including dry resins, plastisol (dispersions in plasticizers), organosol (dispersions in plasticizers plus volatile solvent), and latex (a colloidal dispersion in water used to coat paper, fabric or leather) (U.S. EPA, 1985a).

Properties: (U.S. EPA, 1985a):

Chemical formula	$H_2C=CHCl$
Molecular weight	62.5
Physical state	Gas
Boiling point	-13.3°C
Melting point	-
Density	-
Vapor pressure	2,530 mm Hg at 20°C
Specific gravity	0.91
Water solubility	1.1 g/L water at 28°C
Taste threshold (water)	-
Odor threshold (water)	3.4 mg/L*
Conversion factor (air)	1 ppm = 2.6 mg/m^3

* Amoore and Hautala (1983)

Occurrence

- Vinyl chloride is a synthetic chemical with no natural sources.

- Since 1979, yearly production of vinyl chloride has been approximately 7 billion lbs (U.S. ITC, 1983). Vinyl chloride is polymerized, and little is released to the environment. Environmental releases will be limited to the areas where vinyl chloride is produced and used.

- Vinyl chloride released to the air is degraded in a matter of a few hours (EPA, 1980a). Vinyl chloride released to surface waters migrates to the atmosphere in a few hours or days, where it undergoes photochemical oxidation. Vinyl chloride that is released to the ground does not adsorb onto soil and migrates readily to ground water. Evidence from laboratory studies suggests that vinyl chloride in ground water may degrade to $C0_2$ and Cl- (Vogel and McCarty, 1985). Vinyl chloride is expected to remain in ground water for months to years. Vinyl chloride has been reported to be a degradation product of trichloroethylene and tetrachloroethylene in ground water (Parsons, 1984). Vinyl chloride does not bioaccumulate in individual animals or food chains.

- Vinyl chloride does not occur widely in the environment because of its rapid degradation and limited release. Vinyl chloride is a relatively rare contaminant in ground and surface waters with higher levels found ground water. The Ground Water Supply Survey of drinking water supplies have found that less than 2% of all ground water derived public water systems contain vinyl chloride at levels of 1 µg/L or higher. Vinyl chloride almost always co-occurs with trichloroethylene. Public systems derived from surface water also have been found to contain vinyl chloride but at lower levels. No information on the levels of vinyl chloride in food have been identified. Based upon the limited uses of vinyl chloride and its physical chemical properties, little or no exposure is expected from food. Vinyl chloride occurs in air in urban areas and near the sites of its production and use. Atmospheric concentrations are in the ppt range (U.S. EPA, 1979).

- The major source of exposure to vinyl chloride is from contaminated water.

B. Pharmacokinetics

Absorption

- Vinyl chloride is absorbed rapidly in rats following ingestion and inhalation (Withey, 1976; Duprat et al., 1977).

- Using statistical modeling, Withey and Collins (1976) concluded that, for rats, a total liquid intake containing 20 ppm (wt/wt) vinyl chloride would be equivalent to an inhalation exposure of about 2 ppm (vol/vol) for 24 hours.

Distribution

- Upon either inhalation or ingestion of ^{14}C-vinyl chloride in rats, the greatest amount of ^{14}C activity was found 72 hours after treatment in liver followed by kidney, muscle, lung and fat (Watanabe et al., 1976a,b). Another study of inhalation exposure of rats to ^{14}C-vinyl chloride showed the highest ^{14}C activity immediately after treatment in liver and kidney, followed by spleen and brain (Bolt et al., 1976).

Metabolism

- Bartsch and Montesano (1975) reported two possible metabolic pathways for vinyl chloride, one involving alcohol dehydrogenase, the other involving mixed function oxidase. Hefner et al. (1975) concluded that the dominant pathway at lower exposure levels probably involves alcohol dehydrogenase.

- Vinyl chloride metabolism is saturable (Hefner et al., 1975; Watanabe et al., 1976a, Bolt et al., 1977).

- Chloroethylene oxide, presumably through mixed-function oxidase, may be the main metabolite capable of alkylating intracellular macromolecules (Laib and Bolt, 1977).

Excretion

- Rats administered vinyl chloride by ingestion or inhalation exhale greater amounts of unmetabolized vinyl chloride as the dose is increased (Watanabe et al., 1976a, b).

- Vinyl chloride metabolites are excreted mainly in the urine. In rats, urinary metabolites include N-acetyl-S-(2-hydroxyethylcysteine) and thiodiglycolic acid (Watanabe et al., 1976a).

C. Health Effects

Humans

- Cancer findings in humans are described under *Carcinogenicity*.
- Mutagenic effects in humans are described under *Mutagenicity*.
- Developmental studies in humans are described under *Developmental Effects*.
- At high inhalation exposure levels, e.g., 40-900 ppm (104-2,344 mg/m^3), workers have experienced dizziness, headaches, euphoria and narcosis (U.S. EPA, 1985a).
- Symptoms of chronic inhalation exposure of workers to the vinyl chloride- polyvinyl chloride industry include hepatotoxicity (Marstellar et al. 1975), acro-osteolysis (Lilis et al., 1975), central nervous system disturbances, pulmonary insufficiency, cardiovascular toxicity, and gastrointestinal toxicity (Miller et al., 1975; Selikoff and Hammond, 1975; Suciu et al, 1975). Data on dose-responses in humans are scarce because few measurements of ambient vinyl chloride levels in the workplace were made before 1975 (Mancuso, 1975).

Animals

Short-Term Exposure

- Inhalation exposure to high levels (ca. 100,000 ppm or 260,417 mg/m^3) of vinyl chloride can induce narcosis and death, and, to lower doses, ataxia, narcosis, congestion and edema in lungs and hyperemia in liver in several species (U.S. EPA, 1985a).

Long-Term Exposure

- Administration of vinyl chloride monomer to rats by gavage for 13 weeks resulted in hematologic, biochemical and organ weight effects at doses above 30 mg/kg (Feron et al., 1975).
- Inhalation exposure of rats, guinea pigs, rabbits and dogs to 50 ppm (130 mg/m^3) vinyl chloride, 7 hours/day, 130 exposures in 189 days, did not induce toxicity as judged by appearance, mortality, growth, hematology, liver weight, and pathology. Rats exposed to 100 ppm (260 mg/m^3) 2 hours/day for 6 months, had increased liver weights (Torkelson et al., 1961).

Reproductive Effects

- Potential effects on reproductive capacity have not been studied.

Developmental Effects

- Infante et al. (1976a,b) reported an association between human exposure to vinyl chloride and birth defects and fetal loss, but this association was contradicted by Edmonds et al. (1975) and Hatch et al. (1981).
- Inhalation exposure of rats and rabbits to vinyl chloride concentrations as high as 2,500 ppm (6,500 mg/m^3) on days 6 to 15 (rats) and 6 to 18 (rabbits) of gestation and mice to vinyl chloride levels as high as 500 ppm (1,300 mg/m^3) on days 6 to 15 of gestation did not induce teratogenic effects but did increase skeletal variants in high-dose mice (John et al 1977).
- A developmental effects study with vinyl chloride in rats exposed by inhalation to 600 or 6,000 ppm (2,160 or 21,160 mg/m^3) 4 hours daily on gestation days 9 through 21 was negative for teratogenicity and inconclusive for fetotoxicity (Radike et al., 1977).

Mutagenicity

- Chromosomal effects of vinyl chloride exposure in workers is conflicting in that positive (Ducatmann et al., 1975; Purchase et al., 1975) and negative (Killian et al., 1975; Picciano et al., 1977) results have been reported. Picciano et al. (1977) reported exposures of 0.13 to 15.2 ppm (0.34 to 40 mg/m^3, time-weighted averages) for 1 to 332 months.
- Vinyl chloride is mutagenic, presumably through active metabolites in various systems including metabolically activated systems with *S. typhimurium* (Bartsch et al., 1975); *E. coli* (Greim et al., 1975); yeast (Loprieno et al., 1977); germ cells of *Drosophila* (Verburgt and Vogel, 1977); and Chinese hamster V79 cells (Hubermann et al., 1975).
- Dominant lethal studies with vinyl chloride in CD-1 mice were negative (Anderson et al., 1976).

Carcinogenicity

- Increases in the occurrence of liver angiosarcomas as well as in tumors of the brain, lung, and hematopoietic and lymphopoietic tissues have been associated with occupational exposure to the vinyl chloride-polyvinyl chloride industry in humans (IARC, 1979). The initial report of a link between vinyl chloride exposure and cancer in humans by Creech and Johnson (1974), as well as subsequent reports by others, indicates the high risk and specificity of association with liver angiosarcoma, a very rare tumor in humans.
- Ingestion of vinyl chloride monomer in the diet by rats at feeding levels as low as 1.7 and 5 mg/kg/

day over their lifespan induced hepatocellular carcinomas and liver angiosarcomas, respectively, as well as other adverse hepatic effects (Feron et al., 1981). Til et al. (1983) extended the Feron et al. (1981) work to include lower doses and did not find a significant ($P < 0.05$) increase in carcinogenic effects at feeding levels as high as 0.13 mg/kg/day. Administration of vinyl chloride monomer by gastric intubation for at least 52 weeks resulted in carcinogenic effects in liver and other tissue sites in rats (Feron et al., 1981; Maltoni et al., 1981).

- Chronic inhalation of vinyl chloride has induced cancer in liver and other tissue sites in rats and mice (Lee et al., 1977, 1978; Maltoni et al., 1981).

D. Quantification of Toxicological Effects

The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL\ or\ LOAEL) \times (BW)}{(UF) \times (\_\_\ L/day)}$$

$$= \_\_\_\_\_\ mg/L\ (\_\_\_\_\_\ \mu g/L)$$

where:

NOAEL or LOAEL	=	No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.
BW	=	assumed body weight of a child (10 kg) or an adult (70 kg).
UF	=	uncertainty factor (10, 100, or 1,000), in accordance with NAS/ODW guidelines.
____L/day	=	assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-Day Health Advisory

There are insufficient data for calculation of a One-Day Health Advisory. The Ten-Day HA of 2.6 mg/L is proposed as a conservative estimate for a One-Day HA.

Ten-Day Health Advisory

Inhalation data by Torkelson et al. (1961) were not selected for the Ten-Day HA calculation because of preference for studies with oral exposure. Feron et al. (1975) reported a subchronic toxicity study in which vinyl chloride monomer (VCM) dissolved in soybean oil was administered by gavage to male and female Wistar rats, initially weighing 44 g, at doses of 30, 100, or 300 mg/kg once daily, 6 days per week for 13 weeks. Several hematological, biochemical and organ weight values were significantly ($P < 0.05$ or less) different in both mid- and high-dose animals compared to controls. The NOAEL in this study was identified as 30 mg/kg.

The Ten-Day HA, as well as the One-Day HA, for a 10-kg child is calculated as follows:

$$Ten\ Day - HA = \frac{(30\ mg/kg/day\ (6/7)\ (10\ kg)}{(100)\ (1\ L/day)}$$

$$= 2.6\ mg/L\ (2{,}600\ \mu g/L)$$

where:

30 mg/kg/day	=	NOAEL based on absence of biochemical and organ weight effects in rats exposed orally to vinyl chloride.
6/7	=	expansion of 6 days/week treatment in the Feron et al. (1975) study to 7 days/week to represent daily exposure.
10 kg	=	assumed body weight of a child.
100	=	uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.
1 L/day	=	assumed daily water consumption of a child.

Longer-Term Health Advisory

The Longer-term HA can be calculated from the lifetime feeding study in rats by Til et al. (1983). Til et al. (1983) have extended the earlier work by Feron et al. (1981) to include lower doses with basically the same protocol used in the latter study. Carcinogenic and noncarcinogenic effects were evident with a vinyl chloride dietary level of 1.3 mg/kg/day. At dietary levels of 0.014 and 0.13 mg/kg/day, increased incidences of basophilic foci of cellular alteration in the liver of female rats were evident. However, basophilic foci by themselves are concluded not to represent an adverse effect on the liver in the absence of additional effects indicative of liver lesions such as those found in the 1.3 mg/kg/day group; and a dose-related increase in basophilic foci was not evident. Therefore, the dose of 0.13 mg/kg/day is identified as the NOAEL for noncarcinogenic effects for the Longer-Term HA calculation.

Using the 0.13 mg/kg/day NOAEL from the Til et al. (1983) study, the Longer-term HA for a 10-kg child is calculated as follows:

$$Longer - Term\ HA = \frac{(0.13\ mg/kg/day)\ (10\ kg)}{(100)\ (1\ L/day)}$$

$$= 0.013\ mg/L\ (13\ \mu g/L)$$

where:

0.13 mg/kg/day	=	NOAEL based on absence of adverse liver effects in rats.
10 kg	=	assumed body weight of a child.
100	=	uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.
1 L/day	=	assumed daily water consumption of a child.

The Longer-Term HA for a 70-kg adult is calculated as follows:

$$Longer-Term\ HA = \frac{(0.13\ mg/kg/day)\ (70\ kg)}{(100)\ (2\ L/day)}$$

$$= 0.046\ mg/L\ (46\ \mu g/L)$$

where:

0.13 mg/kg/day	=	NOAEL based on absence of adverse liver effects in rats.
70 kg	=	assumed body weight of an adult.
100	=	uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study
2 L/day	=	assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Because vinyl chloride is classified as a human carcinogen (IARC Group 1 and EPA Group A), a Lifetime Health Advisory is not recommended.

Evaluation of Carcinogenic Potential

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), vinyl chloride may be classified in Group A: Human carcinogen. This category is for agents for which there is sufficient evidence to support the causal association between exposure to the agents and cancer.

- The IARC (1979) has concluded that there is sufficient evidence to classify vinyl chloride as a human carcinogen in its Category 1.

- EPA's Carcinogen Assessment Group (CAG) recently has recalculated its excess carcinogenic risk estimates resulting from lifetime exposure to vinyl chloride through the drinking water (U.S. EPA, 1985a). CAG based its preliminary revised estimates on the Feron et al. (1981) study. The total number of tumors, considering tumors of the lung and liver, in rats exposed through the diet was used to calculate the excess cancer risk. Using the 95% upper limit [$q_1^* = 2.3\ (mg/kg/day)^{-1}$] with the linearized multistage model, they calculated that consuming 2 L of water per day with vinyl chloride concentration of 1.5 µg/L, 0.15 µg/L and 0.015 µg/L would increase the risk of one excess cancer per 10,000 (10^{-4}), 100,000 (10^{-5}) or 1,000,000 (10^{-6}) people exposed, respectively, per lifetime. The CAG is presently reassessing the cancer risk estimate based on the Feron et al. (1981) study by taking into account the more recent data by Til et al. (1983) which, as described previously, is an extension of the earlier Feron et al. (1981) work to include lower doses.

- Maximum likelihood estimates as well as 95% upper limits of cancer risks by the multistage model are presented. Expressing risk as cases/lifetime/person, examples would be 0.01 mg/kg/day or 0.35 mg/L exposure associated with

risks of 1.6×10^{-2} (MLE) and 1.9×10^{-2} (UL) and 0.001 mg/kg/day exposure associated with risks of 1.6×10^{-3} (MLE) and 1.9×10^{-3} (UL).

- Cancer risk estimates (95% upper limit) with other models are presented for comparison with that derived with the multistage. For example, one excess cancer per 1,000,000 (10^{-6}) is associated with exposure to vinyl chloride in drinking water at levels of 50 µg/L (probit), 0.5 g/L (logit), and 0.02 µg/L (Weibull). While recognized as statistically alternative approaches, the range of risks described by using any of these modeling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of consistency of approach and in providing an upper bound on the potential cancer risk, the EPA has recommended use of the linearized multistage approach.

E. Other Criteria, Guidance, and Standards

- The National Academy of Sciences (NAS, 1977) estimated a 10^{-6} risk (95% upper bound estimate) from lifetime exposure to 1 µg vinyl chloride/L drinking water with the multistage model and the lifetime ingestion study in rats by Maltoni et al. (1981).

- The final RMCL by the U.S. EPA Office of Drinking Water is zero, the proposed MCL is 1 µg/L, and the practical quantitation level is 1 µg/L (U.S. EPA, 1985b).

- Ambient water quality criteria (U.S. EPA, 1980b) are 20, 2 and 0.2 µg/L for risks of 10^{-5}, 10^{-6}, and 10^{-7}, respectively, assuming consump-tion of 2 L of water and 6.5 grams of contam-inated fish per day by a 70 kg adult.

- A workplace standard of 1 ppm (time-weighted average) was set by OSHA in 1974 based on the demonstration of angiosarcoma of the liver in vinyl chloride workers (*Federal Register*. 39:35890).

- The ACGIH (1982) has recommended a TLV of 5 ppm (10 mg/m3).

F. Analytical Methods

- Analysis of vinyl chloride is by a purge and trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water (U.S. EPA, 1985c). This method calls for the bubbling of an inert gas through a sample of water and trapping the purged vinyl chloride on an adsorbent material. The adsorbent material is heated to drive off the vinyl chloride onto a gas chromatographic column. This method is applicable to the measurement of vinyl chloride over a concentration range of 0.06 to 1,500 µg/L. Confirmatory analysis for vinyl chloride is by mass spectrometry (U.S. EPA, 1985d). The detection limit for confirmation by mass spectrometry is 0.3 µg/L.

G. Treatment Technologies

- The value of the Henry's Law constant for vinyl chloride (6.4 atm-m^3/mole) suggests aeration as a potential removal technique for vinyl chloride in water (ESE,1984). Removals of up to 99.27% were achieved at 90°C using a pilot packed tower aerator. In similar studies, vinyl chloride removed from ground water using a spray aeration system with total VOC concentration was 100 to 200 µg/L (ESE, 1984). Greater than 99.9% VOC removal was obtained using a four-stage aeration system; each stage employed 20 shower heads with a pressure drop of approx-imately 10 pounds per square inch. In-well aeration has also demonstrated up to 97% removal of vinyl chloride using an air-lift pump. However, practical considerations are likely to limit the application of this (Miltner, 1984).

- The concentration of vinyl chloride in southern Florida ground water declined by 25% to 52% following passage through lime softening basins and filters (Wood and DeMarco, 1980). Since vinyl chloride is a highly volatile compound, it is probably volatilized during treatment (ESE, 1984).

- Adsorption techniques have been less successful than aeration in removing vinyl chloride from water. In a pilot study, water from a ground water treatment plant was passed through a series of four 30-inch granular activated carbon (Filtrasorb 400) columns (Wood and DeMarco, 1980; Symons, 1978); the empty bed contact time was approximately six minutes per column. Influent vinyl chloride concentrations ranged from below detection to 19 µg/L; erratic removal was reported. To maintain effluent concentrations below 0.5 µg/L, the estimated column capacity to breakthrough was 810, 1,250, 2,760 and 2,050 bed volumes for empty bed contact times of 6, 12, 19 and 25 minutes, respectively. In addition, the estimated service life of the activated carbon was low. Similarly, poor removal of vinyl chloride was achieved using an experimental synthetic resin, Ambersorb XE-340, (Symons, 1978).

- Treatment technologies for the removal of vinyl chloride from water have not been extensively evaluated except on an experimental level. Available information suggests aeration merits further investigation. Selection of individual or combinations of technologies to achieve vinyl

chloride removal must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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Sample Risk Assessment and Risk Management Exercises

Introduction to Risk Assessment Case Study on Vinyl Chloride Contamination of Drinking Water

New information on the toxic properties of a widely used chemical, vinyl chloride (VC), has just been published in a major scientific journal. The uses of VC place it under the jurisdiction of EPA, and a senior agency policy maker must decide whether the new information justifies regulatory action. As a first step the policy maker must determine whether and to what extent current uses of VC endanger the public health. The senior policy maker thus assembled a group of top Agency scientists from various disciplines – epidemiology, toxicology, biochemistry, pathology, statistics, chemistry – and posed the following questions:

1. What types of health hazards might be associated with VC, and how well are these known?

2. What is the magnitude of human exposure to VC, and how is the exposure distributed in various population groups?

3. What is the nature and magnitude of human *risk* associated with the various sources of exposure?

The group of scientists collected data to conduct a *risk assessment.* In particular, they developed information to estimate the likelihood that VC will exhibit one or more of its hazardous properties under actual conditions of human exposure. At this stage the senior policy maker is only concerned with understanding the risks of VC and the ways in which that risk can be characterized. The senior policy maker is not presently concerned with what has been referred to as *risk management,* or the issue of how to regulate VC if a risk has been identified. Hence, the senior policy maker is not considering the commercial importance of VC and the possible regulatory consequences of reporting a significant health risk.

The senior policy maker believes strongly that it would not be satisfactory to conclude that no risk assessment could be performed, or that "more research" had to be conducted before any conclusions could be reached. Rather, the senior policy maker felt it was essential that as definitive a statement as was currently possible be made about the health risk of VC, and that the uncertainties in the assessment be identified. The senior policy maker knew it would have to be decided how to handle the scientific uncertainties in the risk management decision, but for now the need was to understand and characterize the current scientific knowledge of the risks of VC.

Your Role

For this exercise, you will play the role of the senior policy maker. Your objective is to ensure that you thoroughly understand the possible health risks associated with various uses of VC and that you can convey your understanding to other people. You are not yet concerned with the ultimate regulatory question of whether and to what extent these uses should be controlled or eliminated; you are concerned with the risk assessment, not risk management.

You will receive various sets of data and analysis from the team of scientists you have assigned to the problem. You will conduct an analysis of the information and its implications for risk. You will review and evaluate the contents of the document. You will be asked to formulate some conclusions based on the data and analysis.

Your review and evaluation will take place within a small working group. After the various issues are aired and discussed, the working group (which collectively represents the senior policy maker)

should reach a consensus on how best to characterize the data and the risk. If a consensus cannot be reached, the alternative views should be expressed. The conclusions of each working group will then be compared and contrasted.

Again, at this stage you are concerned only with risk assessment, not with risk management.

Nature of the Data and Analysis to Be Reviewed

The report contains a discussion of the nature and uses of VC, and the known extent of human exposure to it. The toxicological data on VC will be presented in summary form. You will be asked to examine several issues relating to the data and reach conclusions regarding them. This section constitutes the *Hazard Evaluation.*

The relationship between exposure to VC and the risk of adverse health effects (*Dose-Response Evaluation*) is the next subject. There may be several scientifically plausible options for describing this relationship in the region of human exposure, and you will be asked to judge the relative merits of these various options. That is, you will be asked to choose among them, or formulate a better one.

The third section will contain a summary of data on the *Exposure* of various population groups to VC. Again, several issues arise concerning the interpretation and use of this information, and it will be necessary for the senior policy maker to formulate appropriate conclusions.

In the final step (*Risk Characterization*) you will be asked to present your conclusions regarding the human health risks posed by VC and the uncertainties in your knowledge.

At each of the four major steps of this exercise, issues and data will be presented, and alternative conclusions will be listed. After discussion, you may select the conclusion that seems most appropriate; if none seems appropriate, you should offer your own.

Resource Material

Chapter 3 entitled *Principles of Risk Assessment* provides background material needed to assist your evaluation. You also were given some key principles and additional background material in Chapters 2, 4 and 6.

In addition, each of the following sections contains a discussion of the key principles directly relevant to the specific issues under consideration.

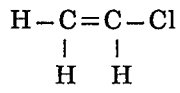
A. Background Information on Vinyl Chloride

Uses of Vinyl Chloride

- Raw Materials - in plastics, rubber, paper, glass and automotive industries.
- Manufacture of - electric wire, insulation and cables, piping, industrial and household equipment, medical supplies, food packaging and building supplies.

Chemical & Physical Properties of Vinyl Chloride

- Structure



- Physical State - Gas
- Stability - Degrades rapidly in the environment
- Solubility in Water - 1.1 g/L at 28°C

Production in U.S.A. - *1983 - 7 billion pounds*

Human Exposure

- General Population - Humans could be exposed to vinyl chloride in drinking water, food, and air. Some people could be exposed also through occupational and consumer usage.
- Worker Populations - Workers are exposed during manufacture.

B. Hazard Evaluation

Some Principles for Hazard Evaluation

- The purpose of hazard evaluation is to identify the types of adverse health effects that may be associated with exposure to VC, and to characterize the quality and strength of evidence supporting this identification.
- The specific hazard of concern in this review is cancer.

- Epidemiological studies in exposed human populations generally are considered to be the best source of information for hazard identification. Unfortunately, they are not available for most substances. Moreover, establishing firm causal links between exposure and human disease is very difficult.

- Studies in experimental animals also provide useful information for hazard identification. Such studies can be controlled, and thus can more easily establish causality. Results from such studies suffer from the obvious limitation that experimental animals are not the species of ultimate interest.

- With one possible exception (arsenic), all known human carcinogens also are carcinogenic in one or more experimental animal species. Many animal carcinogens have not been established as human carcinogens, in most cases because of the lack of adequate epidemiological data.

- There are biological reasons to believe that responses in experimental animals could be mimicked by responses in humans, a proposition supported by considerable empirical data. However, other data show that species differ in response to the same agent.

- It is known that the specific site(s) of tumor formation in humans may be different from that observed in experimental animals.

- Data obtained by administering a substance by the same route of exposure that is experienced by humans are considered more predictive than data obtained by a different route. But if tumors form at internal body sites, the route of exposure may not be important.

- In general, a varied response in experimental animals – tumor formation in several species, both sexes, at several different exposure levels with increasing response at increasing exposure, and at multiple body sites -- provides more convincing evidence of potential human carcinogenicity than does a response that is limited to a single species or sex, or to a single common site of tumor formation.

A number of studies have been conducted in rats, mice and rabbits which show that vinyl chloride is carcinogenic in these species. Statistically significant increases in the numbers of tumors at a variety of sites have been reported following both inhalation and oral exposure.

During the risk assessment case study, we are focusing upon the results of just one of those studies. The reasons for this decision should become clear as you become more acquainted with the data.

The Feron et al. Study

In 1981, an article by Feron et al. entitled "Lifetime Oral Toxicity Study of Vinyl Chloride in Rats" appeared in a respected scientific journal (Food and Cosmetic Toxicology). This paper presented data on the effects in rats of lifetime oral exposure to vinyl chloride. The design of the experiments and the major findings are presented in Tables C-1 and C-2.

Remarks on the Feron et al. Study

1. As far as can be determined from the published Feron et al. article, this study was carefully conducted and there is no reason to doubt the accuracy of the reported data.

2. VC increased the *incidence of risk of tumors* (number of animals with tumors) in all groups of animals given VC in the diet, although the increase in low-dose males was not statistically significant.

3. Rats treated with VC by gavage developed the same tumor types in liver as those treated with VC in the diet, but lung angiosarcomas were not apparent with gavage exposure.

4. Rats developed liver tumors following both dietary and gavage exposures. Lung tumors were produced only by dietary exposure.

5. Following dietary exposure to VC, females showed more neoplastic nodules and hepatocellular carcinomas, whereas males showed more angiosarcomas in liver and lung.

6. Neoplastic nodules and hepatocellular carcinomas were proportionally greater than liver angiosarcomas with dietary exposure to VC, whereas the opposite was evident with gavage exposure to VC.

7. Liver and lung tumors observed in treated animals are rarely formed in untreated (control) rats of the strain (Wistar) used by Feron et al. This is particularly important in the interpretation of liver tumor data in rats treated with VC by gavage as a treatment-related effect.

8. Neoplastic nodules are considered to be a progression towards hepatocellular carcinomas and are, therefore, included in the tumor incidence table. These tumor types are of different cellular origin, and are thus considered distinct tumor types from liver angiosarcomas.

Table C-1. Design of the Feron et al. Study

Species & Route of Exposure	Groups Receiving Vinyl Chloride	# of Animals		Amt. VC Recd. Each Day[1]	Duration of Exp. (weeks)
		Male	Female		
Rat, dietary	Control	60	60	0	104
	Low Dose	60	60	1.7	104
	Mid Dose	60	60	5.0	104
	High Dose	60	60	14.1	104
Rat, gavage	—	60	60	300.0	104

[1] The units of "amount received "are milligrams of vinyl chloride (VC) per kilogram of the animal's body weight.

Note: Gavage is the administration of a substance by means of a stomach tube.

Table C-2. Significant Findings from the Feron et al. Study

Following are the groups in which a statistically significant excess of tumors was found. Complete assessment of tumor formation was made in each sex.

Study Group	Sex	Tumors Found[a]	Tumor Incidence (number of animals with tumors) Control	Low-Dose	Mid-Dose	High-Dose
Rat, dietary	Male	Liver				
		a. neoplastic nodule	0	0	7	24[c]
		b. hepatocellular carcinoma	0	1	2	9[c]
		c. angiosarcoma	0	0	6[c]	27[c]
		Lung				
		a. angiosarcoma	0	0	4[c]	19[c]
Rat, dietary	Female	Liver				
		a. neoplastic nodule	2	26[c]	39[c]	44[c]
		b. hepatocellular carcinoma	0	4	19[c]	29[c]
		c. angiosarcoma	0	0	2	9[c]
		Lung				
		a. angiosarcoma	0	0	1	5[c]
					Dose[b]	
Rat, gavage	Male	Liver				
		a. neoplastic nodule			3	
		b. hepatocellular carcinoma			1	
		c. angiosarcoma			27	
Rat, gavage	Female	Liver				
		a. neoplastic nodule			2	
		b. hepatocellular carcinoma			0	
		c. angiocarcoma			29	

[a] Tumors are described both in terms of target organ and tumor type within the target organ. There are three tumor types distinguished in liver.
[b] There was no matched control group with the treated group given VC by gavage. Thus, statistical comparison could not be done.
[c] A statistically significant excess of tumors relative to untreated control animals. This means that the difference in tumor incidence between the treated and control animals is not likely due to chance. Because the only difference between the control and treated animals was the presence of VC, it is thus likely that the excess tumor incidence is due to this compound. Tumors were found at other sites in both control and treated animals, but no others occurred in statistically significant excess.

9. Identification of tumor types in each animal individually was not given. Therefore, for the purpose of quantitative risk assessment, animals with hepatocellular carcinoma also are assumed to have neoplastic nodules. Therefore, only neoplastic nodules and angiosarcomas are added together to derive total liver tumors.

Issues to Be Considered by the Senior Policy Maker

1. How do these data conform (or not conform) to the principles laid out on pages C-2 and C-3 particularly the last one?

2. In view of these principles, is there any reason to conclude that VC is not carcinogenic in rats of both sexes (by dietary and gavage exposures)?

3. Is there any reason to believe that humans would not be at risk of developing these various tumors, assuming they were exposed to VC?

4. Is there any way to determine, from the data given, whether responses in humans are likely to be similar to those of rats? Males or females?

5. Should the liver tumors be considered relevant to humans?

6. Should the data obtained by gavage treatment be considered relevant to human exposure?

Conclusions Regarding VC Carcinogenicity

Which of the following conclusions best characterize the evidence you have seen?

1. VC is a human carcinogen.

2. VC is a probable human carcinogen.

3. VC is a carcinogen at several sites in rats of both sexes, by both dietary and oral routes of administration. VC is thus a human carcinogen and is expected to increase the incidence of lung and liver tumors in the exposed human population.

4. VC is a carcinogen at several sites in rats of both sexes. VC is thus a probable human carcinogen, although only humans exposed orally are likely to be at risk. Data obtained when VC was administered by stomach tube are not relevant to any route of human exposure. Thus, exposure through other routes has no identifiable risk for humans.

5. Although VC is carcinogenic in rats, no data suggest that it is carcinogenic in humans. The animal data provide only weak evidence that VC may be a human carcinogen.

6. Because of the extreme conditions under which tumors were produced in these animal experiments, there is no reason to believe VC is a possible human carcinogen.

7. Other (formulate your own conclusion).

C. Dose-Response Evaluation

The General Problem and Principles Guiding Approaches to Its Solution

Because of the relative complexity of dose-response evaluation, the following discussion is substituted for a statement of key principles.

Recall that animal data showing that a chemical is carcinogenic usually are obtained in the high exposure region of the dose-response curve: Thus, animal exposures were in the 1.7 to 300 mg/kg/day ranges (Table C-1). Human exposure is in the range of 0.03 to 2.0 µg/kg/day over a range of potential drinking water concentration levels (Table C-5). What can be said about risks in the range of human exposure?

At least three general approaches to this problem have been proposed by various experts.

Approach 1

Based on general theories of how carcinogens act to produce cancer (largely derived from experimental studies and epidemiological data), all finite exposure levels will produce a finite risk. The magnitude of the risk will decline as the magnitude of exposure declines (this is even clear in the animal data).[1]

If the quantitative relationship between exposure and risk were known for all exposures, risk to rodents exposed at very low levels could be predicted from the measured exposure-risk data. Risks to humans could be predicted at these very low levels if the relationship between rodent and human susceptibilities were known. Although these relationships cannot be known with accuracy, a plausible *upper limit* on human risk can be predicted with sufficient accuracy to be used as a guide to making risk decisions. Actual human risk is not likely to exceed the upper limit (although it may), and it may be less.

[1] These two sentences are the proper formulation of the "no-threshold" concept. The "no-threshold" concept does not mean that all finite exposures *will cause* cancer; instead, it means that all finite exposures will increase the probability that cancer will occur.

Approach 2

The quantitative relationships between high exposure and low exposure risks in rodents and between rodent and human risk are not known with sufficient reliability to be used in risk assessment. Moreover, there is no reliable theory on which it can be concluded with assurance that low-level human exposure (i.e., exposure below the range producing detectable risks) poses any risk at all. As with other toxic effects, carcinogenicity will not be initiated within an individual until a minimum threshold of exposure is exceeded. In such circumstances, the only reasonable course is to report the magnitude of the margin of safety (MOS) by which humans are protected. MOS is the maximum amount of exposure producing no measurable tumorigenic response in animals divided by the actual amount of human exposure. MOS gives the risk manager adequate information on which to decide whether exposures must be reduced or eliminated to provide human protection. A relatively large MOS is desirable because it is likely that the threshold for the entire human population is substantially lower than that observed in small groups of experimental animals.

Approach 3

Although there is adequate theory and some evidence to permit the conclusion that humans are at finite risk at all finite exposure levels, there is insufficient knowledge to allow prediction of the risk in quantitative terms. The risk assessor should simply attempt to describe risks qualitatively, perhaps coupling this description with some information on the potency of the compound and the magnitude of human exposure. This type of presentation is adequate for the risk manager, who should not be concerned with the quantitative magnitude of risk in any case.

Each of these views, and perhaps others as well, has some merit. It would seem that the first approach, if correct, would provide the most useful approach for decision making. Indeed, it is the approach now used by EPA and other agencies as well. EPA and the other agencies emphasize that the predicted numerical risks are not known to be accurate, but, because of the nature of the models used to predict them, they are likely to be *upper-bound estimates of human risk.* An *upper-bound estimate* is one that is not likely to be lower than the true risk.

For this exercise we shall estimate low exposure risks using the model currently used by EPA. A model is a mathematical formula that describes the relationships between various measures. Two models are needed to predict low exposure risk:

- *A high-to-low exposure extrapolation model* is needed to predict low exposure risks to rodents from the *measured* high exposure-high risk data (Table C-2). EPA currently uses a so-called *linearized multistage model* for this purpose. This model is based on *general* (not chemical-specific), widely held theories of the biological processes underlying carcinogenesis. Application of the model to the rodent exposure risk data produces an estimate of the *lifetime risk for each unit of exposure* in the low exposure region. This is called the *unit cancer risk.* The "linearized" model is used to ensure that the unit cancer risk is an *upper bound on risk.*

- An *interspecies extrapolation model* is used to extrapolate from rodent unit risks to human unit risks. There are empirical data and theory to support EPA's current use of the assumption that rodents and humans are at equal risk at the same exposure measured in milligrams of carcinogen per square meter of body surface area per day.

EPA's selection of these models is based on the agency's view that they are the best supported for purposes of deriving an upper Bound estimate of risk. Alternative models are available for both these forms of extrapolation and cannot be ruled out. In most cases, but not always, use of plausible alternative models will yield lower estimates of risk than those predicted by the two described here. Differences can sometimes be very large, but in most cases differences are relatively small, especially when the models are limited to those that are linear at low exposure.

Further discussions of various models and their plausibility can be found in the resource material.

Approach Taken for This Exercise

In this exercise we reveal the upper bound of unit cancer risks predicted for VC using the models currently preferred by EPA. The effect of using alternative, plausible models is also described.

Estimates of Upper Bound, Lifetime Unit Cancer Risks Using Current EPA Models

Application of the EPA models for high-to-low dose and interspecies extrapolation to the measured animal cancer data of Table C-2 yields the results shown in Table C-3.

Estimates of Lifetime Unit Cancer Risks Using Other Models

Application of *other models for high-to-low dose extrapolation* usually yields unit risks equal to or slightly lower than those in Table C-3, as long as the other models incorporate the concept that risk increases in direct proportion to exposure in the low exposure region (linear models).

Table C-3. Upper Bounds on Lifetime Unit Cancer Risks Predicted from Application of EPA's Preferred Model to Tumor Data, Table C-2

Species, Sex	Route of Exposure	Tumor Site	Unit Cancer Risk[1]
Rat, male	Diet	Lung	0.11
Rat, male	Diet	Liver	0.3
Rat, male	Diet	All tumors	0.29
Rat, female	Diet	Lung	0.058
Rat, female	Diet	Liver	1.9
Rat, female	Diet	All tumors	2.3

[1]Risk for an average daily lifetime exposure of 1 unit. Units are same as those used earlier for describing the animal exposure (Table C-1) and the human exposure (Table C-5) (mg/kg bw/day). Risk is obtained from unit risk by multiplying the latter by the actual number of units of human exposure; the higher the unit risk, the higher the risk.

Adoption of certain nonlinear models for high-to-low dose extrapolation predicts risk about 1,000 to 10,000 times lower than those predicted by use of the EPA model. The nonlinear models are not widely recommended.

Dose-Response Evaluation Not Involving Formal Extrapolation

For those who believe formal extrapolation beyond the measurable dose-response data should not be performed, it is important to identify the exposures at which VC produces tumors and those at which no tumor excess is found (the "No-Observed-Effect Level" or NOEL). Table C-4 identifies NOELs from data in Table C-2.

Issues to Be Considered by the Senior Policy Maker

1. Which of the three possible approaches should be taken? Explicit estimate of risk? Quantitative estimate of MOS? Qualitative descriptions only? Should other approaches be considered?

2. If explicit estimates of unit risks are made, should only EPA's currently preferred models be used? Should the results of applying other models also be displayed?

3. Which species/sex/tumor site data from Table C-3 should be used for unit risk assessment? All, shown individually as in Table C-3? Only the data set yielding the highest unit risk? A sum of all? Other?

4. How should the uncertainties in use of models be described?

5. Are the observed NOELs true "no-effect" levels? Could they simply reflect the fact that in experiments with relatively small numbers of animals, the failure to observe a statistically significant increase of tumors is an artifact of the experimental design, and not a true absence of biological effect? How should this uncertainty, if it is real, be taken into account?

Alternative Conclusions Regarding Dose-Response Evaluation

1. The unit cancer risks listed in Table C-3 are true upper bound estimates. The true unit risk is not likely to exceed those determined, may be lower, and could be zero.

2. The same as the first conclusion, but add: The use of alternative, plausible models yields unit risks about 10 to 100 times lower than those from Table C-3.

3. Unit risks should be reported for all plausible models, and the full range of estimates should be reported without bias.

4. There is no justification for calculating and reporting unit risks. What is critical for understanding the public health importance of low level exposure to VC is the margin of safety (MOS). Estimation of the is based on the NOELs for its carcinogenic effects; these figures are reported in Table C-4.

Table C-4. No-Observed-Effect Levels (NOELs) for Chronic Exposure to VC

Study Group	Sex	Tumor	NOEL[1]
Rat, dietary	Male	Liver	1.7
Rat, dietary	Female	Liver	None found
Rat, dietary	Male	Lung	1.7
Rat, dietary	Female	Lung	5.0
Rat, gavage	Male	Liver	None found
Rat, gavage	Female	Liver	None found

[1] Units are expressed as mg/kg bw/day. "None found" means that a measurable excess of tumors was not found at all levels of exposure used in the experiment.

5. Neither unit cancer risks nor NOELs are reliable indicators of human risk,and neither should be considered for risk assessment. Dose-response relations for the human population are not known for VC; risk should be described in qualitative terms only.

6. Other (formulate your own conclusion).

D. Human Exposure Evaluation

Some Principles for Exposure Evaluation

- The purpose of the exposure evaluation is to identify the magnitude of human exposure to VC, the frequency and duration of that exposure, and the routes by which humans are exposed. The number of exposed people also must be identified, along with other characteristics of the exposed population (e.g., age and sex).

- Exposure may be based upon measurement of the amount of VC in various media (air, water, food) and knowledge of the amount of human intake of these media per unit of time (usually per day) under different conditions of activity.

- Some individuals may be exposed by contact with several media. It is important to consider total intake from all media in such situations.

- Because only a limited number of samples of various media can be taken for measurement, the representativeness of measured values of environmental contaminants are always uncertain. If a sampling is planned adequately, the degree to which data for a given medium are representa-tive of that medium usually can be known.

- Sometimes air levels of pollutants can be estimated by the use of mathematical models. Although some of these models are known to be predictive in many cases, they are not thought to be so in other cases.

- Standard average values and ranges for human intake of various media are available and generally are used unless data for specific agents indicate such values are inappropriate.

Available Information on Vinyl Chloride

The following information has been summarized from the human exposure section of the Office of Drinking Water Criteria Document on Vinyl Chloride. Use this information in formulating your risk assessment decision.

Humans may be exposed to vinyl chloride in drinking water, air, and food. This analysis is confined to these three media since they are considered to be general sources common to all individuals. Some individuals may be exposed to VC from sources other than those cited here, notably in occupational settings and from the use of consumer products containing vinyl chloride.

Unfortunately, data and methods to estimate exposure of identifiable population subgroups from all sources simultaneously have not yet been developed. To the extent possible, estimates are provided of the number of individuals exposed to each medium at various VC concentrations. The 70 kg adult male is used for estimating intake.

Water

Cumulative estimates of the U.S. populations exposed to various VC levels in drinking water from public drinking water systems are presented in Table C-5. Of the approximately 1.3 million people exposed to levels ranging from 1 to 5 µg/L, 0.9 million (65%) obtain water from surface supplies. All exposure to VC in drinking water at levels above 5 µg/L is expected to be from ground-water sources.

No data were obtained on regional variations in the concentration of VC in drinking water. The highest concentrations are expected to be near sites of polyvinyl chloride production.

Table C-5 also shows daily intake levels of VC in drinking water estimated at various exposure levels. The data in the table suggest that the majority of the persons using public water supplies would be exposed to intake levels below 0.028 µg/kg bw/day.

Table C-5. Estimated Drinking Water Intake of Vinyl Chloride

	Persons using supplies exposed at indicated levels		
Exposure level (µg/L)	Population	% of total population	Intake (µg/kg/day)
≥ 1	1,922,000	0.9%	≥ 0.028
> 5	591,000	0.3%	>0.14
> 10	118,000	0.1%	>0.29
> 50	118,000	0.1%	>1.4
> 70	0	0	>2.0

Assumptions: 70-kg adult male, 2 L of water per day

Diet

No data were obtained on levels of VC found in foods in the United States. Therefore, no estimates of the daily intake of VC from the U.S. diet could be made.

Air

Exposure to vinyl chloride in the atmosphere varies from one location to another. The highest level of VC reported in the atmosphere was 2,100 µg/m^3. High levels (> 15 µg/m^3) have been detected in other areas. Normal levels, however, are somewhat lower. Brodzinsky and Singh (1982) calculated a median air level of 0.0 ng/m^3 (0.0 µg/m^3) in each of three types of areas: rural/remote, urban/suburban, and source-dominated.

The monitoring data are not sufficient to determine regional variations in the exposure levels.

Table C-6 describes the daily respiratory intake of VC from air as estimated using the assumptions present-ed and the maximum and minimum ambient levels reported above. Intake calculated using the maxim-um VC level reported is 690 µg/kg/day; few, if any, persons are believed to be exposed to that level. Estimated daily intake under other circumstances is estimated to be 0 µg/kg/day.

Table C-6. Estimated Respiratory Intake of Vinyl Chloride

Exposure (µg/m³)	Intake (µg/kg/day)
Rural/remote (0.0)	0
Urban/suburban (0.0)	0
Source dominated (0.0)	0
Maximum (2100)	690

Assumptions: 70 kg adult male; 23 m³ of air inhaled/day (ICRP, 1975)

Issues to Be Considered by the Policy Maker

- Is there any reason to believe that animal data obtained from continuous lifetime exposure should not be used to characterize the risk to people exposed intermittently?

Conclusions Regarding Human Exposure to Vinyl Chloride

1. Although the estimates for air and water are based upon different data and different assumptions, these data are adequate for assessing vinyl chloride risks. The risk manager should be made aware of the uncertainties in each of the data sets.

2. In addition to conclusion #1, it should be noted that all the exposures should be added because some people will be exposed to all sources of vinyl chloride.

3. None of the exposure estimates is adequate for use in risk assessment. The risk assess-ment should describe exposure in qualitative terms only. Such a qualitative description is appropriate and adequate for characterizing risk, which also can be done in qualitative terms only.

4. Other (formulate your own conclusion).

E. Risk Characterization

Purpose

In the last step of risk assessment, the information collected and analyzed in the first three steps is integrated to characterize the risks to humans. In line with the alternative ap-proaches for describing dose-response relations, at least three approaches can be taken to this step.

1. Provide an explicit numerical estimate of risk for each population group by multiplying the unit risk *times* the number of units of exposure experienced by each group:

   (unit cancer risk) x (units of exposure) = risk

   In this equation, risk is unitless – it is a probability.

   Equation:

   Unit risk x Ingestion volume x Body weight x Conversion of mg to µg x Unit(s) of exposure

2. Provide an estimate of the MOS for each group by dividing the NOEL by the exposure experienced by that group.

3. Describe risks qualitatively for each of the population groups.

Risk characterization also might include some combination of all three approaches, along with a description of their relative merits.

It also is essential that the statistical and biological uncertainties in estimating the extent of health effects be described in this step.

Attached you will find a discussion of Unit Risk Assessment for Vinyl Chloride. This document describes the use of Feron et al. data for the estimation of a unit risk for oral exposure to vinyl chloride.

In Table C-7, the risks for each population group using data from Table C-5 are reported. These risks are based on the *highest* unit cancer risk described in the attached discussion ($a_1^* = 2.3$ (mg/kg/day)$^{-1}$ for all tumors combined. If other unit risk figures from Table C-3 had been used, somewhat lower risks would result. And, if unit cancer risks derived from other dose-response models had been used, the risks shown may be 10 to 100 times lower. The risks in Table C-7 are thought to be upper-bound lifetime risks.

Issues to Be Considered by the Senior Policy Maker

1. Are the results reported in Table C-7 an adequate characterization of VC risks? What else should be added?

2. Should risks derived from all the unit risks reported in Table C-3, the attached discussion and unit risks obtained using alternative models also be reported?

Table C-7. Risks in Each Population Group for Risk Characterization

Source	Risk	Size of Population Group	Upper Bound on Number of Cancer Cases over Lifetime
Drinking Water alone			
0 µg/L	0	220 million +	0
1 µg/L	7×10^{-5}	1.9 million +	133
5 µg/L	3×10^{-4}	591,000	177
10 µg/L	7×10^{-4}	118,000	83
50 µg/L	3×10^{-3}	118,000	354
70 µg/L	5×10^{-3}	0	0

3. The risks and number of cases reported in Table C-7 depend on the assumption that the number of people exposed and their level of exposure will remain constant over a lifetime. Is this a plausible assumption? Can alternative assumptions be used?

4. Is it important to distinguish routes of exposure? Should unit risks obtained from the inhalation data be used only for population groups exposed by inhalation? Should gavage data be used at all?

5. Is it important to know whether a finite risk exists at all exposure levels, or whether a threshold exists?

6. Is it appropriate to estimate the number of cancer cases expected by multiplying risk times population size (last column of Table C-7)? What is more important -- risk to an individual, or risk to a population?

7. What are the biological and statistical uncertainties in estimating the number of expected cancer cases? How should they be estimated and described?

Alternative Conclusions

1. Upper-bound risks to humans exposed to VC are those reported in Table C-7. Although risks obtained from the use of other models may be lower, the risks could be as high as those reported in Table C-7.

2. The risks shown in Table C-7, as well as those obtained from use of all other plausible models and all of the various tumor site data, should be reported, and all estimates should be given equal weight. Such a presentation affords the decision maker a view of the uncertainty in the estimated risks.

3. Upper-bound estimates of lifetime risks to humans are those reported in Table C-7. Use of all other animal data sets and alternative, plausible risk models would result in prediction of lower risks, perhaps up to 100 times lower. These risks are conditional on the assumption the VC is a probable human carcinogen, based solely on observations of carcinogenicity in several species of experimental animals. Uncertainties in exposure and population estimates are those described in the exposure assessment section.

4. VC is a probable human carcinogen, based on observations of carcinogenicity in more than one animal species. Exposures needed to produce animal carcinogenicity are many thousands of times higher than those to which humans are exposed. The margins of safety by which humans are protected are shown in Table C-7. Because a NOEL has not been identified for all the various carcinogenic endpoints, a greater than usual MOS should be employed to protect human beings.

5. VC is a probable human carcinogen, based on observations of carcinogenicity in more than one species of animals. Humans may be exposed through air, water, and during employment. In general, small numbers of people may be exposed continuously to very low levels of VC, and a few groups are exposed intermittently. The individual risk in the general population is probably low to moderate, but this translates to a relatively large number of cancer cases because of the large population size, etc.

6. Other? Some combination of the others?

Attached Discussion to Aid Risk Assessors

Unit Risk Assessment for Vinyl Chloride

The data used to estimate a unit risk for oral exposure to vinyl chloride are based on the Feron et al. (1981) study. The statistically significant increases reported for liver and lung tumors were considered biologically significant. For the liver tumors, neoplastic nodules were considered a progression toward hepatocellular carcinomas, and these are included in the analysis in Tables C-8 and C-9. Extrapolations using the linearized multistage model show values of q^*_1 for the individual tumors ranging from 8.8×10^{-2} to 1.3×10^{-1} for the males and from 5.8×10^{-2} to 1.3 for the females. The value of q^*_1 based on males was 3.0×10^{-1} for liver tumors and 2.9×10^{-1} based on all tumors combined. For the females the value of q^*_1 based on liver tumors was 1.9 and for all tumors combined was 2.3. All units of q^*_1 are per mg/kg/day.

Before proceeding with the unit risk estimates, we will explain, the total tumor counts in Tables C-8 and C-9. For the liver, all animals with hepatocellular carcinomas were assumed to also have the neoplastic nodules. Thus, only the neoplastic nodules and liver angiosarcomas were added to derive the total liver tumors. Otherwise, the totals would have exceeded the number of animals examined. Also, in adding the lung and liver tumors, the totals were not allowed to exceed one less than the number examined.

The result of this latter restriction was to raise the value of q^*_1 slightly due to increased variance. In fitting the response data in Tables C-8 and C-9 with the human equivalent dosages, the human equivalent dosages were derived by dividing the corresponding animal dosages by $(W_h/W_a)^{1/3}$. The human weight (W_h) was assumed to be 70 kg; the male rats were estimated to weigh 350 g and the female rats were estimated to weigh 200 g (Figure C-1). Thus, the corresponding human equivalent dosages were 0, 0.29, 0.85, and 2.41 mg/kg/day based on the male rats, and 0, 0.24, 0.71, and 2 mg/kg/day based on the female rats.

When the response and human equivalent dose data were fit to the linearized multistage model, the 95% upper limit on the largest linear term (Table C-9) was:

$$q^*_1 = 2.3 \text{ (mg/kg/day)}^{-1}$$

To derive an estimate of the 95% lower level of concentration, d, corresponding to a 95% upper level of risk, R, the following equation is used:

$$R = 1\text{-}e^{-q^*d_1}$$

where d is the lower limit on dose in mg/kg/day. To solve for d in µg/L, we use the transformation

$$1 \text{ mg/kg/day} \times (70 \text{ kg}/2 \text{ L}) \times 1{,}000 \text{ µg/mg} = 35{,}000 \text{ µg/L}$$

If we set $R = 10^{-5}$ then

$$d = (35{,}000/q^*_1) \ln (1\text{-}10^{-5}) \text{ (µg/L)}.$$

For the highest value of $q^*_1 = 2.3$ (mg/kg/day)$^{-1}$ (Table C-9), setting $R = 10^{-5}$ yields a value of d = 0.15 µg/L. Setting $R = 10^{-4}$ or 10^{-6} yields values of d = 1.5 µg/L and d = 0.015 µg/L, respectively. For comparison purposes only we compare the potency of vinyl chloride by the diet versus the inhalation routes. A previous memo we sent you estimated the 95% upper limit of potency for VCM as $q^*_1 = 1.7 \times 10^{-2}$ (mg/kg /day)$^{-1}$ based on an inhalation study showing angio-sarcomas and other tumors in rats. That potency estimate vas derived for water quality criterion purposes. In that document an inhalation to inges-tion by gavage relationship of 1 ppm inhaled = 2.28 mg/kg/day ingested was derived for 200 g rats based on VCM uptake study. Without that adjustment for route differences, a direct transformation based on a 70 kg human breathing 20 m^3/day would have yielded a 1 ppm inhaled = 0.76 mg/kg/day relationship and a $q^*_1 = 5.2 \times 10^{-2}$ mg/kg/day, still 44 times less than the estimate from the diet study.

In summary, the VCM potency estimates are reported in Table C-10.

Introduction to the Risk Management Case Study

You are a group of experts called together by the water supply manager of a small town to advise her on a possible case of drinking water contamination. You will be required to analyze the situation and make a brief presentation of your findings at a public meeting. Earlier you were presented with information concerning the health risks associated with exposure to the three compounds. You are aware that, although the risk assessment is fairly complete, there are a host of other factors that must be considered in implementing a permanent solution. These factors will be a part of your risk management problem. While risk assessment considers the nature of the risk, risk management must consider taking appropriate action to alleviate that risk.

Most of you probably are familiar with the work of Dr. John Snow in London, 1854. Dr. Snow, through a very thorough epidemiological study, proved that the Broad Street pump was the source of an outbreak of cholera. He did this by statistically correlating incidence of disease with exposure to drinking water at that well. This example was an early form of risk assessment. Later, Snow removed the handle from

Table C-8. Type and Incidence of Statistically Significant Treatment-Related Changes in the Liver and Lung of Male Wistar Rats Exposed to VCM in the Diet. Values of q^*_1 and Concentration from Multistage Extrapolation Model Included

	Treatment Group (mg/kg/day)					95% Lower-Limit Concentration Associated with Risk (µg/L)[b]		
	0	1.7	5.0	14.1	q^*_1[a] $(mg/kg/day)^{-1}$	10^{-4}	10^{-5}	10^{-6}
Number of rats examined[c]	55	58	56	59				
Liver								
Neoplastic nodules	0	1	7	23	2.1×10^{-1}	16.7	1.7	0.2
Hepatocellular carcinomas	0	1	2	8	8.8×10^{-2}	39.8	4.0	0.4
Angiosarcomas	0	0	6	27	1.3×10^{-1}	27.0	2.7	0.3
Total liver tumors[d]	0	2	13	50	3.0×10^{-1}	11.7	1.2	0.1
Lung								
Angiosarcomas	0	0	4	19	1.1×10^{-1}	31.8	3.2	0.3
Total animals with tumors[e]	0	2	17	58	2.9×10^{-1}	12.1	1.2	0.1

[a] Human equivalent $q^*_1 = q^*_1$ (a) $(W_h/W_a)^{\frac{1}{3}}$ in $(mg/kg/day)^{-1}$.
[b] Concentration in µg/L = $(-35{,}000/q^*_1)$ ln (1-R).
[c] Found dead or killed in extremis or terminally.
[d] Sum of neoplastic nodules and liver angiosarcomas..
[e] Total must be at least less than total examined.

Table C-9. Type and Incidence of Statistically Significant Treatment-Related Changes in the Liver and Lung of Female Wistar Rats Exposed to VCM in the Diet. Values of q*1 and Concentration from Multistage Extrapolation Model Included

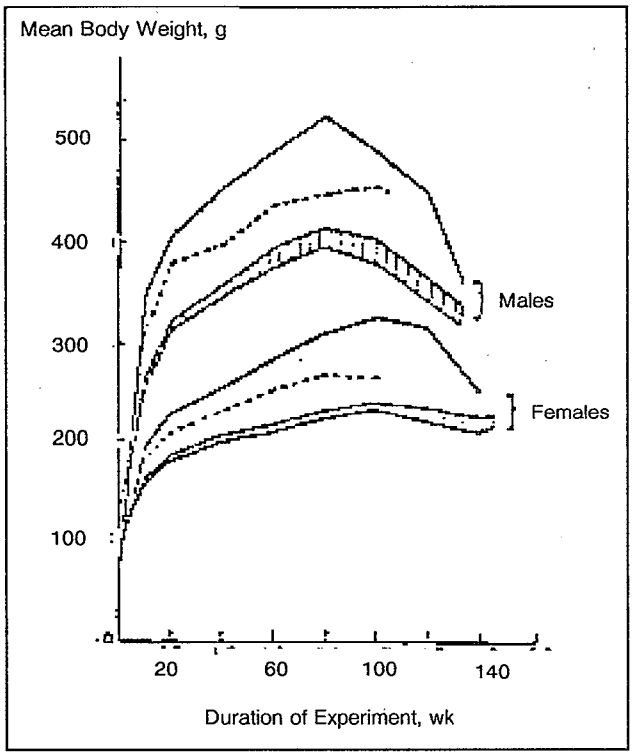
	Treatment Group (mg/kg/day)					95% Lower-Limit Concentration Associated with Risk (µg/L)[b]		
	0	1.7	5.0	14.1	q^*_1[a] $(mg/kg/day)^{-1}$	10^{-4}	10^{-5}	10^{-6}
Number of rats examined[c]	57	58	59	57				
Liver								
Neoplastic nodules	2	26	39	44	1.3	2.7	0.3	0.03
Hepatocellular carcinomas	0	4	19	29	5.0×10^{-1}	70.0	0.7	0.07
Angiosarcomas	0	0	2	9	8.8×10^{-2}	39.8	4.0	0.4
Total liver tumors[d]	2	26	41	53	1.9	1.8	0.2	0.02
Lung								
Angiosarcomas	0	0	1	5	5.8×10^{-2}	60.3	6.0	0.6
Total animals with tumors[e]	2	26	42	56	2.3	1.5	0.2	0.02

[a] Human equivalent $q^*_1 = q^*_1$ (a) $(W_h/W_a)^{\frac{1}{3}}$ in $(mg/kg/day)^{-1}$.
[b] Concentration in µg/L = $(-35{,}000/q^*_1)$ ln (1-R).
[c] Found dead or killed in extremis or terminally.
[d] Sum of neoplastic nodules and liver angiosarcomas..
[e] Total must be at least less than total examined.

Table C-10. VCM Potency Estimates

Route	Potency q^*_1 (mg/kg/day)$^{-1}$	95% Lower-Limit Concentration Associated with Risk (µg/L) 10^{-4}	10^{-5}	10^{-6}
Oral				
Based on diet study	2.3	1.5	0.15	0.015
Based on inhalation study	1.7×10^{-2}	200	20.0	2.0
Inhalation				
Based on inhalation study	5.2×10^{-2}	67.3	6.7	0.7

Figure C-1. Average Body Weights of the Extra Controls Fed the 10%-PVC Diet ad Libitum (-) and of the Rats Given 300 mg VCM/kg Body Weight in Oil by Gavagea



[a] The weight curves of the rats receiving 0, 1.7, 5.0, or 14.1 mg VCM/kg body weight/day from the 10% PVC diets fed for 4 hours each day all lie within the shaded area.
Adapted from Feron et al., 1981.

the pump and observed that, as the people drank water from other sources, the incidence of cholera declined. This later act was what we are calling risk management. Dr. Snow took positive action to correct the problem. Unfortunately, today's drinking water contamination problems are not solved as readily.

Snow had a relatively simple problem to solve by modern standards, but remember, he accomplished this twenty years prior to the discovery of the germ theory of disease by Koch and Pasteur. The public health aspect of drinking water has come upon the reverse of Snow's problem. He knew the risk of drinking water from the Broad Street pump, but could not identify the contaminant.

Today we can identify many more contaminants, but are unable to determine the exact nature of the potential adverse human health effects. Further, quantifying those risks is itself a risky business. Projection of human risk exposure from data on animal carcinogens would appear to be straight-forward. But, as you saw in the risk assessment problem, even the "experts" cannot agree on validity of extrapolation of animal data to human health risks. Even the most experienced scientists cannot predict the exact nature of the risk of exposure to chemical contaminants.

In the problem described here, the risk assessment would likely conclude that one contaminant is an animal carcinogen, another, a human carcinogen, and the third, a neurotoxin. Large uncertainties surround the projection of human risks from animal data. Six or more orders of magnitude (10^6 or one million times) of uncertainty are associated with the use of models extrapolating animal data to human data. Everyone would feel more comfortable if there were more certainty in the risk assessment, but there is very seldom a straight answer to a chemical contaminant safety issue. All of this uncertainty becomes part of the evaluation and analysis conducted in the process called risk management.

Your Role

You, as an expert consultant, must advise the town manager and recommend an appropriate course of action to protect the public health, both long and short term. Specifically, you are concerned with mitigating people's exposure to the toxic chemicals in drinking water.

This case study focuses on your ability to use the information presented in this course to solve a drinking water contamination problem. The review

and evaluation will take place with a group of 10 to 15 people. You will realize that there is no one right or wrong answer and common sense should prevail. The *process* by which you arrive at your conclusions is very important. The group should attempt to come to a consensus about what action can be taken. If you cannot come to a consensus, present the alternative views. The conclusions of each work group will be compared and contrasted at a final plenary session.

Nature of the Material

You will focus on several types of information. Results of the previously completed risk assessments will be reviewed briefly. In addition, both qualitative and quantitative information will be provided on various courses of action. This information will include political and social factors as veil as treatment, economic and environmental data. You must consider the interests of various economic and public interest groups in your recommendation.

The case study package is divided into five sections. and you have available the Health Advisory documents for aldicarb, vinyl chloride and trichloroethylene. The Health Advisory documents contain occurrence, health effects, analytical chemistry and treatment data on each chemical. Use this information as appropriate in formulating your response to the questions that appear in the latter sections of the case study. The discussion of drinking water regulations focuses on proposed rulemaking for the volatile synthetic organic chemicals and some pertinent legislative background. This information should prove useful in organizing your thoughts, but should not be viewed as providing the exact answer or constraining your response. Remember, this is proposed rulemaking and you are required to respond immediately. The following three sections provide site-specific information, questions to be answered, and calculations to be performed. It might be helpful if someone in each group could provide a calculator, but this is not required. We also will provide a facilitator for each group. He should not lecture, nor should you look to him to provide answers.

The focus of this exercise is risk management and risk communication. Try to use the conclusions from your risk assessment of the relevant chemicals, as well as the information provided here and in the lectures.

A. Background Information on Chemicals

The Health Advisories for aldicarb, trichloroethylene, and vinyl chloride are located. Table C-11 provides helpful information for working through this problem. Additional information concerning the chemicals will appear as appropriate throughout this document and in some of the lecture outlines.

B. Drinking Water Regulations: Statutory and Institutional Concerns

Introduction

In thinking about how to manage a drinking water contamination incident, you should understand the framework provided by the Safe Drinking Water Act as amended through 1986. This Act provides a two Step approach to setting drinking water standards. The first step is to set a *maximum contaminant level goal (MCLG)*, formerly called the *recommended maximum contaminant level (RMCL)*. EPA must also set the *maximum contaminant level (MCL)* as close to the MCLG as is feasible. Simply put, MCLGs are health-based goals and MCLs are technology-based standards. Standards are enforceable and goals are not.

MCLGs are nonenforceable health goals. MCLGs are "set at the level at which no known or anticipated adverse effects on the health of persons occur and which allow an adequate margin of safety." The House Report on the Safe Drinking Water Act provides Congressional guidance on developing RMCLs (MCLGs):

> ...the recommended maximum level must be set to prevent the occurrence of any known or anticipated adverse effect. It must include an adequate margin of safety, unless there is no safe threshold for a contaminant. In such a case, the recommended maximum contaminant level should be set at zero level.

The RMCLs (MCLGs) for a number of carcinogenic volatile organic chemicals were proposed at zero based on this language. Obviously, the MCL or enforceable level cannot be zero since zero cannot be measured. The MCL or enforceable level must be a non-zero number.

The MCL must be set as close to the RMCL (MCLG) as is feasible. "Feasible" means with the use of the best technology, treatment techniques, and other means available, taking cost into consideration. The 1986 Amendments include language indicating that these technologies must be tested under field conditions. The Amendments also state that technologies for the control of *synthetic organic chemicals* (SOCs) must be at least as effective as granular activated carbon.

The general approach used in setting MCLs for the volatile organic chemicals (VOCs) or any other contaminant is to determine feasibility. This requires an evaluation of: (1) the availability and cost of analytical methods, (2) the availability and performance of treatment technologies, and (3) an evaluation of the cost and feasibility of achieving various levels. A brief nontechnical description of each component of the regulatory analysis follows.

Table C-11. Information from Health Advisories and Analyses of Water Wells

Chemical	Aldicarb	Trichlorethylene	Vinyl Chloride
Use/State	Pesticide solid	Solvent/degreaser liquid	Manufacturing additive/gas
Health Effect	Colinesterase inhibitor/CNS	Animal carcinogen	Human carcinogen
Class	D	B2	A
Route of Exposure/ Occurrence	Oral, dermal/ applied to soil and crops, found in ground water	Ingestion, inhalation, used widely to degrease machinery, found in ground water	Oral, inhalation,almost always co-occurs with TCE, found in ground water
Chemical Concentration	30 ppb (µg/L)	60 ppb	20 ppb
Recommended Standards	1-Day HA = 10 µg/L (for 10-kg child) Lifetime HA with rel. source cont. of 20% = 10 µg/L	2.8 µg/L concentration would produce a cancer risk of 1 x 10^{-6} or 1 in a million	.015 µg/L concentration would produce a cancer risk of 1 in one million (1 x 10^{-6}) 2.6 µg/L short term HA
Detection Limits	1.3 µg/L	0.2 µg/L	0.3 µg/L
Level Down to Which to Treat			
Short-term Treatment	Bottled water point of use device for truck in water	bottled water carbon adsorption, boil water with adequate	bottled water ventilation
Longer-term Treatment	Granular activated carbon (GAC) adsorption with sulfone & sulfoxide by products taken into consideration	GAC/Aeration	Aeration

Analytical Methods

The analytical method constraints include considerations of precision and accuracy at low (ppb or parts per billion) levels. The numbers produced by the analyst must be within some reasonable proximity of the true value (*accuracy*) and must be reproducible (*precision*).

The analytical methods for the volatile organic chemicals include *gas chromatography* (GC) with either conventional detectors or a *mass spectro-meter* (GC/MS). These analytical methods use the *purge and trap technique* for extraction from the liquid phase and concentration on a column containing a sorbent. The higher-molecular-weight organic chemicals (e.g., pesticides) generally require extraction with a solvent (e.g., hexane or methylene chloride). The sample or solvent extract is injected into the entrance port of the GC column. Purging of the volatile chemicals is accomplished using an inert gas. The organic chemicals of interest are then sorbed to the wall or special packing material within the column. The compounds are desorbed from the column by heating and backflushed into the head of the GC column. This is followed by separation of constituents in the GC column and measurement with a specific detection system. Detection systems include *photoionization and electrolytic conductivity.* The detection system generates an electrical signal which is amplified and transformed to a peak on a stripchart recorder. The position and height of the peak is then compared to internal standards for identification and quantification.

Each step of this process is subject to some error. These errors are expressed as precision and accuracy. For the single lab this is sufficient. But, in developing national standards, interlaboratory variability must be considered. In general, EPA defines the *method detection limit* (MDL) as the minimum concentration of a substance that can be measured and reported with 99 percent confidence that the true value is not zero. This detection limit differs for different labs, different instruments, different analysts, and is not necessarily reproducible over time if all these factors remain the same. Traditionally, quantification limits are five to ten times the method detection limit. The importance of this is that it is not possible to determine compliance or noncompliance with an

MCL unless there is reasonable assurance that the reported value is close to the true value.

The remaining component of the use of analytical measurements in solving drinking water contamination problems is that of acceptable laboratory performance. The criteria for EPA certified labs for the types of gas chromatography (GC) analyses under consideration in this problem are ± 40 percent at concentrations under 10 µg/L and ±20 percent at concentrations above 100 µg/L. Consider these limitations in determining what levels will be acceptable in solving the case study problem.

Treatment Technologies

Once the lowest level that can be quantified has been determined, the next constraint for determination of the MCL is the performance of the *best available technology* (BAT). The obvious first step would be to list all technologies that have ever been used to remove a particular compound or class of contaminants. For example, for the volatile organic chemicals, there are data available on *ozonation, ultraviolet irradiation, aeration and adsorption.* Conventional coagulation and softening treatment provides little to no removal of these compounds. However, there is limited evidence that ozonation and ultraviolet irradiation can break down chlorinated ethylenes and other organic molecules with double bonds. The kinetics of oxidation of organic contaminants is not understood well enough to determine the cost of various levels of removal.

Packed tower aeration and, to a lesser extent, granular activated carbon (GAC) adsorption, have been shown to be highly effective (>99.9% removal) for the removal of volatile organic chemicals. The BAT determination for the volatile organic chemicals is then based on these two processes.

Aeration Treatment

The performance potential of a properly designed packed tower aeration system is quite good for VOC removal. Both field and laboratory experiments and theoretical calculations indicate that at the concentrations generally found in drinking water (a few hundred parts per billion or less), aeration can produce treated water with sub-parts per billion concentrations. Aeration processes provide a fixed percent removal of contaminants. As a consequence the concentration in the treated water can be affected by fluctuations in the raw water concentration. Volatile organic chemical contamination of ground waters is generally due to poor waste disposal practices and many times the exact source can never be found. The hydrogeological factors affecting the fate and transport of these chemicals are complex. Modeling them is an inexact science. As a result, historic information on changes in concentrations should be considered in the design of an aeration treatment system. Traditionally, a safety factor of two times the raw water concentration has been used in a conservative design. If these and other design factors are properly considered, the treated water should meet a concentration goal below the analytical quantification levels.

Transfer of volatile organic chemicals from air to water might be a concern depending on the proximity to human habitation, treatment plant worker exposure, local air quality, local meteorological conditions, daily volume of water processed and the concentration of the contaminant. EPA evaluated a number of existing and planned packed tower installations using an air dispersion/human exposure model. The results of this evaluation indicated that lifetime exposure to small amounts of carcinogenic chemicals in air did not result in a significant increase in individual risk of cancer (generally, less than one in 106 or 107). These were the highest risks and occurred for persons exposed to 70 years of worst-case air concentration conditions at less than 200 meters from the source. As the distance grows, the population exposed increases, but the concentration declines so rapidly that projected cancer risks become very small. Using very conservative assumptions, these kinds of analyses resulted in a projection of less than one possible cancer incidence nation wide over 70 years. Since drinking water contaminated with the carcinogenic chemicals of concern was the projected cause of approximately 50 excess cases of cancer, air emissions from aeration treatment facilities are not a major national concern.

If necessary, control of volatile organic chemical emissions from packed tower aeration installations is feasible using air phase GAC adsorption. EPA currently has full-scale field evaluations of this technology under way. Preliminary evidence indicates that installation of this equipment would approximately double the cost of water treated by packed tower aeration.

GAC Adsorption Treatment

GAC adsorption removal of most organic contaminants from drinking water, especially ground waters, is very good. There are a few exceptions, including low-molecular-weight compounds such as vinyl chloride. Experiments with this chemical have shown removal from water to be erratic using GAC adsorption columns.

The capacity of carbon for removing a contaminant from water can be determined empirically. Generally, GAC adsorption removes the contaminant to below its detection limit until the capacity of the fixed bed adsorber is reached. The point at which the contaminant is detected in the effluent water is

termed breakthrough. After breakthrough the GAC may remain in service for some time until the treatment goal is reached. Carbon is replaced at intervals of 3 to 6 months or longer in practice.

Background organics, sometimes measured as total organic carbon or TOC, can increase the amount of carbon required to treat a given volume of water. This is especially a problem in surface waters. But, since the volatile organic chemicals do not occur often above one part per billion in surface waters, this may not become a major issue. It also should be noted that empirical determination of carbon usage rates at the site takes into account the competitive effects of background naturally occurring organics (i.e., TOC).

Once the treated water goal is reached by a GAC treatment system, the carbon must be replaced or reactivated. Small systems generally have a contract with a supplier who delivers fresh carbon and removes the spent carbon. The supplier may then reactivate the carbon far use in waste water treatment. Larger systems can reactivate the GAC on-site using heat. Fluidized bed reactivation furnaces are popular for this taste. This thermal reactivation process can result in the discharge of particulates and com-bustion products of both the fuel and the adsorbed organics to air. Experiments at Cincinnati, Ohio, revealed that toxic (carcinogenic) dioxins were in the stack gases of the reactivation furnace. After-burners typically installed with reactivation furnaces remove the dioxins and other air pollutants. These concerns are not likely to limit the applicability of GAC adsorption as BAT for the control of organic chemical contaminants in water.

Cost Considerations

The Safe Drinking Water Act requires EPA to take cost into consideration in setting standards. The maximum contaminant level will be set as close to the goal (zero for carcinogens) as is feasible taking cost into consideration. Tables C-12 and C-13 contain cost estimates for 99% removal of nine volatile organic chemicals using GAC and aeration. For perspective, the average cost of treated drinking water in the U.S. ranges from about 1 dollar to a $1.50 per 1,000 gallons. Table C-14 shows the cost of removing trichloro-ethylene to various concentrations. Notice that the rate of increase of cost does not change dramatically as the percent removal increases, nor are the actual costs significantly higher than that paid for treated water today. The cost of removing volatile organic chemicals down to the analytical quantification level is thererfore seemingly reasonable.

At the national level, total national costs are an obvious concern. Table C-16 presents a summary of the national cost as a function of the selection of maxi-mum contaminant level. These data show that, as the level decreases, the total number of systems required to treat increases and consequently the cost increas-es. The total national cost was not the major determ-inant in the selection of the maximum contaminant level, but was considered in the overall analysis.

Final Rule

The final rule promulgating maximum contaminant levels for the nine volatile organic chemicals has not been published. The EPA may change the numbers or the methodology used in determining those numbers. The solution to the risk management problem should consider that regulations for trichloroethylene and vinyl chloride are due out shortly and that a rule for aldicarb and other pesticides is also forthcoming. But, do not restrict your response to what EPA may or may not do. In other words, you must take the Health Advisory and risk assessment/management problem data and develop your own solutions and numerical goals.

Table C-12. Cost for 99 percent removal (from 500 µg/L to 5 ug/L) of the nine VOCs using packed tower aeration in August 1983 dollars

Compound	Costs by System Size Category* 100-500 (0.037 MGD)	3,300-10,000 (0.95 MGD)	100,000-500,000 (36.8 MGD)
Trichloroethylene			
Capital cost	69,000	264,000	4,789,000
Annual O & M cost	1,400	18,000	617,000
Total cost (¢/100 gallons	79.0	15.5	9.4
Tetrachloroethylene			
Capital cost	67,000	252,000	4,607,000
Annual O & M cost	1,200	15,000	513,000
Total cost (¢/1,000 gallons)	75.0	14.2	8.4
Carbon tetrachloride			
Capital cost	66,000	249,000	4,536,000
Annual O & M cost	1,200	15,000	509,000
Total cost (¢/1,000 gallons)	75.0	14.0	8.3
1,2-Dichloroethane			
Capital cost	84,000	461,000	10,221,000
Annual O & M cost	2,400	37,000	1,149,000
Total cost (¢/1,000 gallons)	101.0	28.5	18.7
Vinyl chloride			
Capital cost	60,000	201,000	3,453,000
Annual O & M cost	900	11,000	377,000
Total cost (¢/1,000 gallons)	66.0	11.0	6.2
1,1-Dichloroethylene			
Capital cost	64,000	229,000	3,975,000
Annual O & M cost	1,000	13,000	428,000
Total cost (¢/1,000 gallons)	71.0	12.5	7.1
Benzene			
Capital cost	74,000	325,000	6,538,000
Annual O & M cost	1,700	23,000	781,000
Total cost (¢/1,000 gallons)	86.0	19.2	12.3
p-Dichlorobenzene (1,000 ug/1 to 750 ug/1)			
Capital cost	51,000	146,000	2,489,000
Annual O & M cost	700	8,000	283,000
Total cost (¢/1,000 gallons)	56.0	8.1	4.6
1,1,1-Trichloroethane (500 ug/1 to 200 ug/1)			
Capital cost	52,000	150,000	2,500,000
Annual O & M costs	700	8,500	290,000
Total cost (¢/1,000 gallons)	57.0	8.2	4.7

*Number of persons served and million gallons per day

Table C-13. Cost for 99 percent removal (from 500 µg/1 to 5 µg/1) of the nine VOCs using granular activated carbon adsorption in August 1983 dollars

Compound	Costs by System Size Category*		
	100-500 (0.037 MGD)	3300-10,000 (0.95 MGD)	100,000-500,000 (36.8 MGD)
Trichloroethylene			
Capital cost	24,000	240,000	9,000,000
Annual O & M cost	4,500	86,000	710,000
Total cost (¢/100 gallons)	57.0	34.0	14.0
Tetrachloroethylene			
Capital cost	24,000	240,000	7,700,000
Annual O & M cost	2,800	45,000	400,000
Total cost (¢/1,000 gallons)	45.0	22.0	11.0
Carbon tetrachloride			
Capital cost	24,000	240,000	9,800,000
Annual O & M cost	5,700	85,000	930,000
Total cost (¢/1,000 gallons)	66.0	34.0	17.0
1,2-Dichloroethane			
Capital cost	24,000	240,000	11,000,000
Annual O & M cost	9,400	150,000	1,500,00
Total cost (¢/1,000 gallons)	93.0	52.0	23.0
Vinyl chloride			
Capital cost	NA	NA	NA
Annual O & M cost	NA	NA	NA
Total cost (¢/1,000 gallons)	NA	NA	NA
1,1-Dichloroethylene			
Capital cost	24,000	240,000	9,100,000
Annual O & M cost	4,600	90,000	740,000
Total cost (¢/1,000 gallons)	58.0	35.0	15.0
Benzene			
Capital cost	24,000	236,000	17,200,000
Annual O & M cost	15,00	258,000	2,800,000
Total cost (¢/1000 gallons)	150	83.3	37.6
p-Dichlorobenzene (1000 ug/L to 750 ug/L)			
Capital cost	24,000	240,000	5,100,000
Annual O & M cost	1,900	22,000	230,000
Total cost (¢/1000 gallons)	38.0	15.0	6.9
1,1,1-Trichloroethane (500 ug/L to 200 ug/L)			
Capital cost	24,000	240,000	10,000,000
Annual O & M costs	6,600	100,000	1,100,000
Total cost (¢/1000 gallons)	73.0	38.0	18.0

*Number of persons served and million gallons per day

Table C-14. Comparison of Various Levels of Removal of Trichloroethylene (as percent versus total costs (cents per thousand gallons)

% removed	Total Cost (cents per thousand gallons)	
	Using packed tower aeration	Using GAC adsorption
50	5.9	18.5
90	8.5	22.7
99	12.0	25.3

Table C-15. Summary of Impacts of the Regulatory Options for Controlling Volatile Organic Chemicals (Federal Register, November 13, 1985, p.46927)

	Regulatory Options		
	1 µg/L	5 µg/L	10 µg/L
Number of Systems Impacted	3,800	1,300	800
Cost of Control			
Total cost ($M)	1,300	280	150
Annual cost ($M)	100	21	11
Cost of Monitoring			
Compliance ($M)	—	9	—
Unregulated ($ M) (1445)	—	2	—
Annual cost per Family ($)			
Very small (25-500)	96	91	90
Small (501-3300)	47	41	40
Medium (3301-50k)	12	12	11
Large (>50k)			
Annual Cancer Cases Avoided	42	32	31

Table C-16. Costs Impacts of MCLs at Various Levels

MCL Opts. µg/L	Estimated # Systems Impacted	National Cost ($ millions)		Annual Cost per Family per Size of System (dollars per year)			
		Total capital	Annual	Very small	Small	Medium	Large
1	3,800	1,300	100	96	47	12	8
5	1,300	280	21	91	41	12	3
10	800	150	11	90	42	11	1

C. Background on the Contaminated Water Supply System

Existing Water System

Population served: 30,000 people

Capacity: 5.1 MGD

Average demand: 3.0 MGD

Maximum day demand: 4.2 MGD

Source:
- three wells approximately 500 feet deep
- capacity of each well is 1.8 MGD
- screened between 400 - 500 feet with gravel pack
- 18" steel casing from 0 - 400 feet
- portland cement grout from 0 - 200 feet
- all wells are pumped to a common manifold that flows to the water treatment plant
- soil profile: 0 - 100 ft., sandy soil; 100 - 400 ft., sand clay mixture; 400 - 500 ft., wet sand and gravel; 500 ft. , bedrock

Storage: 3.5 million gallons

Treatment: Iron removal using chlorine oxidation, alum coagulation, sedimentation, and rapid pressure sand filtration. Disinfection (chlorine), fluoridation and corrosion control (lime and metallic phosphates) are also practiced.

Constructed: 1957

Mechanical/Structural Condition: Excellent

Indebtedness: None

Rates:
- $1.05 per thousand gallons—commercial/industrial
- $0.85 per thousand gallons—residential

Major Employers:
- printing plant (50 people)
- potato farming (4000 acres)
- machinery manufacturing (20 people)
- shopping center (30 people)
- plastic bag manufacturer (10 people)
- soda bottler (50 people)
- US Air Force Base (10,000 including residents)

All of the above employers are on the town water system (except the Air Force base) and are within three miles of the water wells. The Air Force base has its own drinking water treatment plant, which is supplied by a surface water source.

Water Quality Results

The analyses on the following page were reported by the State Health Department lab. Since then, repeat samples have been analyzed and the results were not found to be significantly different. The health officer wants you to notify the public immediately, but will not tell you what to say. He says that no one should use the water because it contains carcinogens and other toxic chemicals. This is not all that acceptable to the town government, since they cannot provide an alternate water supply in a short time frame.

D. Determining Human Exposure and Risks

Exposure

In order for human health effects to occur as a result of environmental contamination, the level of exposure to the contaminant must be high enough to reach the target organs in toxic concentrations. Some systems have been designed to directly measure human exposure to potentially harmful agents, but they are not generally available for situations like this. Exposure to possible toxins in drinking water cannot be determined precisely in the general population.

In the case at hand, we have three contaminants, two of which are volatile synthetic organic chemicals normally used in industry and one is an agricultural pesticide. This opens up a number of possible means and routes of exposure for various individuals. First, a number of people might be exposed to trichloroethylene in the work place, since it is frequently used to degrease machinery parts. Agricultural workers might be expose to aldicarb during application to the fields. These are specialized subpopulations who might be considered in determining the "safe" dose for the general population. We might have to do some research to find approximations for the exposures in the work place.

- Should we consider occupational exposures in determining a "safe" level in drinking water?
- Which people might be receiving occupational exposure? (see major employers list). Why?

Parameter	Well #1 raw	Well #1 treat	Well #2 raw	Well #2 treat	Well #3 raw	Well #3 treat
Iron (mg/L)	3.0	0.05	2.2	0.05	2.0	0.05
pH	6.0	7.8	5.9	7.8	6.2	7.8
Alkalinity (mg/L)	10	110	14	110	12	110
Vinyl chloride (µg/L)	40	20	14	20	6	20
Trichloroethylene (µg/L)	50	60	30	60	100	60
Aldicarb (total) µg/L	30	30	30	30	30	30
Total Organic Carbon (mg/L)	3.0	1.0	2.1	1.0	1.0	1.0

Concentrating on exposure in the home, we have three major routes of exposure: breathing, oral consumption, and dermal exposure. We generally assume that the average adult drinks 2 L per day and breathes 20 cubic meters of air. Another standard assumption for volatile contaminants is half of the exposure is due to volatilization.

- For which contaminants might sources of exposure other than drinking water be a concern? Name the sources. What are the routes?
- Would a 20% relative source contribution from drinking water be a satisfactory assumption in this case?
- Is there any way for the residents to mitigate some of the exposure? Would boiling the water help? How should the boiling be done?
- The town has a central sewer system with an activated sludge treatment system. The activated sludge process includes 4 to 5 hours of vigorous aeration of the waste water. What is the ultimate sink (air, water, or land) for each contaminant?

Risks

In the risk assessment case study and the risk communication video tape you learned some basic principles that now need to be applied to risk management.

- In layman terms, describe the individual and population risks incurred from various sources of exposure. Describe the fate and transport of the contaminants and the relationship of this to the human risk of disease.
- How did you calculate individual and population risks for this exercise?
- What are your target numbers for correction?
- How would you quantitate and articulate the uncertainties surrounding your risk estimates?

V. Options Available for Reducing Risk

Short-Term

- Point-of-use carbon treatment units @ $400 per year per home.
- Bottled water delivered to the doorstep @ $600 per home per year.
- Issue a boil water order @ $ 0 per year.
- Do nothing @ $ 0 per year.

Long-Term

- Regional water supply with the Air Force @ $500,000 per year (this water contains an annual average concentration of 98 µg/L of total trihalomethanes).
- Drill new wells @ $200,000 per year (extensive studies would be required to find an uncontaminated source).
- Install point-of-entry GAC adsorption treatment units in each home @ $1,000,000 per year.
- Install central GAC treatment to meet the following levels of trichloroethylene:

  1.0 µg/L @ 19.5 cents per thousand gallons
  5.0 µg/L @ 19.3 cents per thousand gallons
  25.0 µg/L @ 19.0 cents per thousand gallons

- Install central packed tower aeration treatment to meet the following levels of trichloroethylene:

  1.0 µg/L @ 5.0 cents per thousand gallons
  5.0 µg/L @ 2.9 cents per thousand gallons
  25.0 µg/L @ 3.7 cents per thousand gallons

- Install central packed tower aeration and GAC adsorption to meet the following levels of trichlorethylene and aldicarb:

  1.0 µg/L @ 22.1 cents per thousand gallons
  5.0 µg/L @ 20.0 cents per thousand gallons
  10.0 µg/L @ 18.3 cents per thousand gallons

Questions

- Which short and long term option (one of each) would you select? Why?

- What is the total annual cost of each selected option?

- What are some possible secondary impacts of the selected options?

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