EPA/625/4-89/024
June 1990

Seminar Publication

Risk Assessment, Management and Communication of Drinking Water Contamination

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Washington, DC

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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 cover 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

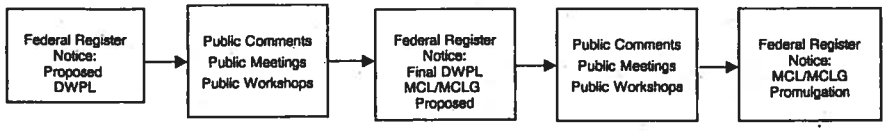
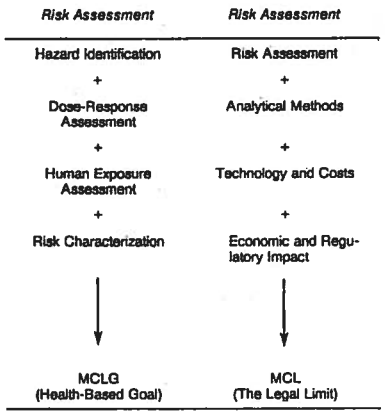


Figure 2-2. MCL/MCLG development



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) (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:

- 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 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.
- 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 ground-water 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 2-8. 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 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 [illegible]: 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 2-9. 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-Trichloroberizene
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.

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.

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 gastroenteritis.

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.
>
> 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

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.

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.

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)

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 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.

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.

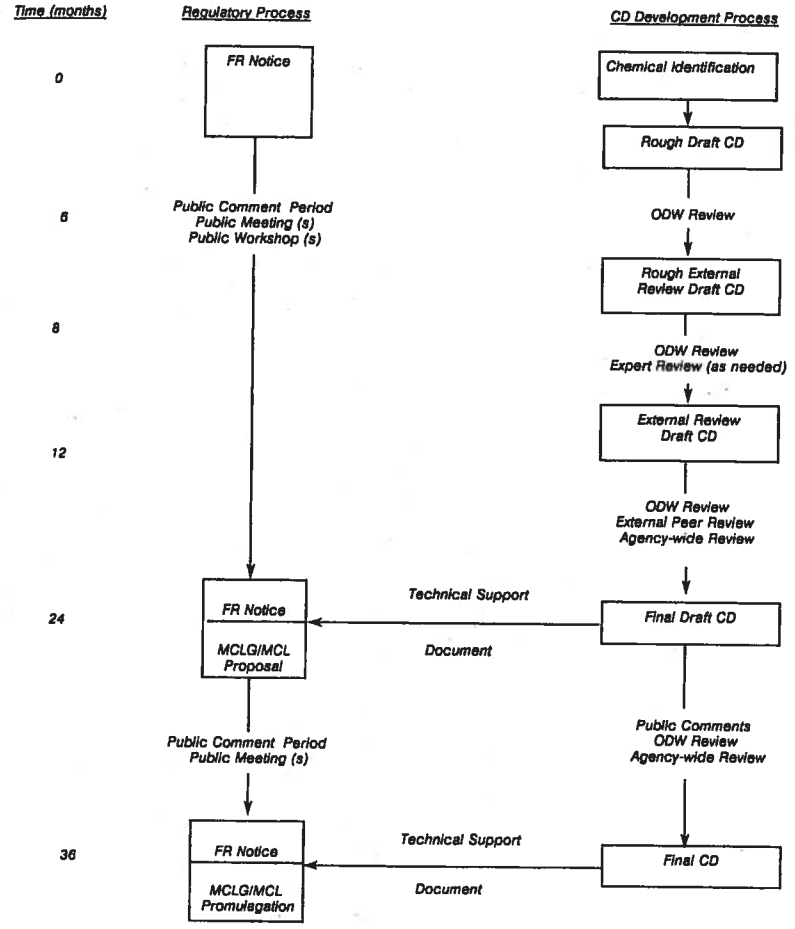
2.4 Criteria Documents

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.

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,

6) [illegible] 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 subpopulation(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 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 en[illegible]ble 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.

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.

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 longe[illegible] HA is generally derived from a study of [illegible]ubchronic 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.

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

Exposed 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 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:

Lifetime HA = DWEL × 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 Advi

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 2-18. 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
Delapon	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 a 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 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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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 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 L… Species of Rat for a Group o… 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

...se 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 reversibili... some cases, an adverse health effect will disapp... 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.

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 ... 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

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 histopathology or clinical chemistry (except in the dog)	• Albino rabbits used • Area of application is free of hair and abraded • If substance 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 application	• Rabbits used • Place liquid or unmoistened 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 - Bushler occluded patch - Magnusson and Kligman maximization	• 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, histopathology, etc.	• Typical protocol: - 90 days (13 weeks) duration - 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 having a tumor of a certain type) are due to random variations in tumor incidence or to exposure to the substance.

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 stillborn - 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 resorbed 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 (F0) 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

-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.

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.

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.

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

l 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.

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).

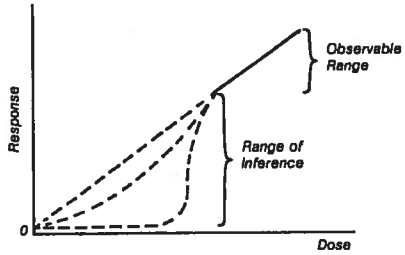
Although there is no effect at 125 mg/kg/day, the response is nevertheless compatible with a risk of about 0.05 (5 percent) because of the statistical uncertainties associated with the small numbers of animals used.

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

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

Model Applied	Lifetime Risk (1.0 mg/kg/day)
One-hit	6.0×10^{-6} (1 in 17,000)
Multistage	6.0×10^{-8} (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.

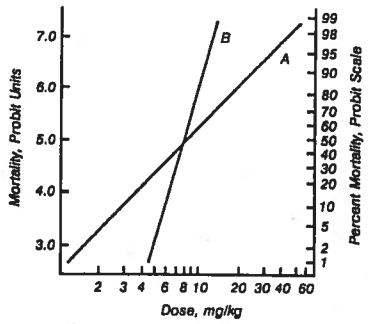
3.3.2.3 *Slope of the Dose-Response*

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.

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

...o 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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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

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.