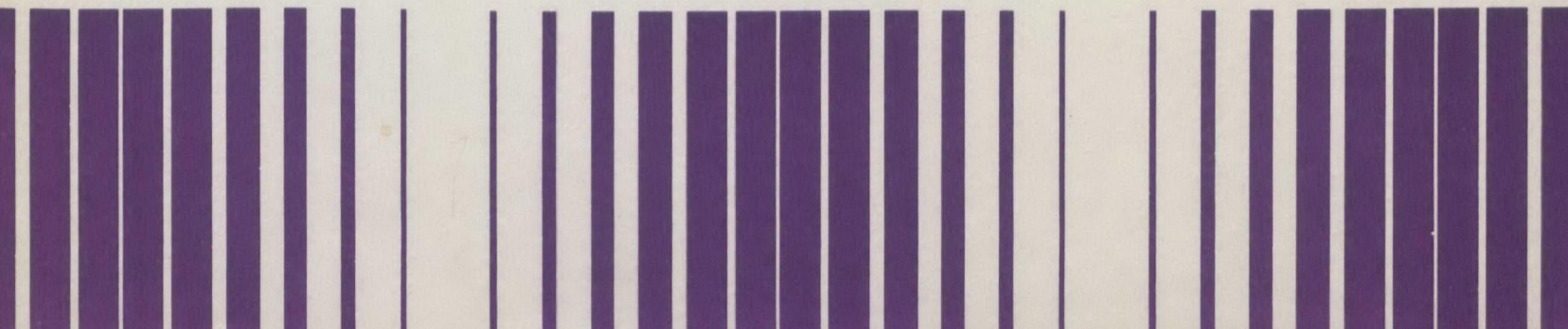**⊕EPA**

Technology Transfer

Workshops on Assessment and Management of Drinking Water Contamination

Revised March 1987

♻EPA

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

CENTER FOR ENVIRONMENTAL
RESEARCH INFORMATION
CINCINNATI, OHIO 45268

OFFICE OF DRINKING WATER
WASHINGTON, DC 20460

TECHNOLOGY TRANSFER

WORKSHOPS ON ASSESSMENT AND MANAGEMENT

OF DRINKING WATER CONTAMINATION

WORKSHOP ON RISK ASSESSMENT AND MANAGEMENT OF DRINKING WATER CONTAMINATION

INTRODUCTION -- STATEMENT OF PURPOSE

Every week the news media bombard us with reports of toxic wastes threatening our environment, especially our drinking water supplies. The topic of this seminar is how one identifies, assesses and manages the occurrence of potentially toxic chemicals in drinking water. Obviously, one cannot become an expert in the toxicology, chemistry and treatment aspects in a two or three day seminar. Rather, the intent of this workshop is to present a broad range of relevant information from the fields of toxicology, chemistry and engineering to assist the workshop participants in assessing and managing drinking water contamination problems.

This will be accomplished through a series of lectures on U.S. EPA programs, toxicology, chemistry and treatment principles. There also will be an opportunity for the workshop attendees to participate in group exercises on particular risk assessment and management problems that center around specific ODW Health Advisory chemicals. It is hoped that a broad spectrum of academic and employment backgrounds among the participants will make these exercises interesting and informative.

Finally, a videotape explaining how to handle media coverage and risk communication will be presented. The emphasis here will be on the analysis of actual new reels and how the water supply or health official might handle media contacts during an emergency situation.

Because of the short time frame and the large quantity of information, each attendee will be required to accomplish some reading on his or her own time during the course of the seminar. It is essential that each person arrives at the risk assessment and risk management group sessions well prepared and ready to participate. A facilitator will be there to help each group, but it is not our intention that this person will lecture. We do expect each person to take part in the solutions of the problems.

We hope that by the closing of this workshop, each participant will be able to better handle similar problems occurring in that partici- pant's own Region, State or locality and that the procedures laid out in this workshop will improve the quality of his or her performance on the job.

PART I

EPA's OFFICE OF DRINKING WATER's DEVELOPMENT OF STANDARDS

AND

HEALTH ADVISORY PROGRAM

A. Glossary of Terms
B. Toxicological Approaches for Developing National Drinking Water
     Standards and Health Advisories
C. EPA's Health Advisory Program

A. GLOSSARY OF TERMS

Risk Assessment and Management

Absorbed dose. The amount of a chemical that enters the body of an exposed organism.

Absorption. The uptake of water or dissolved chemicals by a cell or an organism.

Absorption factor. The fraction of a chemical making contact with an organism that is absorbed by the organism.

Acceptable daily intake (ADI). Estimate of the largest amount of chemical to which a person can be exposed on a daily basis that is not anticipated to result in adverse effects (usually expressed in mg/kg/day). (Synonymous with RfD)

Active transport. An energy-expending mechanism by which a cell moves a chemical across the cell membrane from a point of lower concentration to a point of higher concentration, against the diffusion gradient.

Acute. Occurring over a short period of time; used to describe brief exposures and effects which appear promptly after exposure.

Additive Effect. Combined effect of two or more chemicals equal to the sum of their individual effects.

Adsorption. The process by which chemicals are held on the surface of a mineral or soil particle. Compare with absorption.

Ambient. Environmental or surrounding conditions.

Animal studies. Investigations using animals as surrogates for humans, on the expectation that results in animals are pertinent to humans.

Antagonism. Interference or inhibition of the effect of one chemical by the action of another chemical.

Assay. A test for a particular chemical or effect.

Bias. An inadequacy in experimental design that leads to results or conclusions not representative of the population under study.

Bioaccumulation. The retention and concentration of a substance by an organism.

Bioassay. Test which determines the effect of a chemical on a living organism.

1

Bioconcentration. The accumulation of a chemical in tissues of an
    organism (such as fish) to levels that are greater than the level
    in the medium (such as water) in which the organism resides (see
    bioaccumulation).

Biodegradation. Decomposition of a substance into more elementary
    compounds by the action of microorganisms such as bacteria.

Biotransformation. Conversion of a substance into other compounds by
    organisms; includes biodegradation.

bw. Body weight.

CAG. Carcinogen Assessment Group.

Cancer. A disease characterized by the rapid and uncontrolled growth
    of aberrent cells into malignant tumors.

Carcinogen. A chemical which causes or induces cancer.

CAS registration number. A number assigned by the Chemical Abstracts
    Service to identify a chemical.

Central nervous system. Portion of the nervous system which consists
    of the brain and spinal cord; CNS.

Chronic. Occurring over a long period of time, either continuously or
    intermittently; used to describe ongoing exposures and effects
    that develop only after a long exposure.

Chronic exposure. Long-term, low level exposure to a toxic chemical.

Clinical studies. Studies of humans suffering from symptoms induced by
    chemical exposure.

Confounding factors. Variables other than chemical exposure level
    which can affect the incidence or degree of a parameter being
    measured.

Cost/benefit analysis. A quantitative evaluation of the costs which
    would be incurred versus the overall benefits to society of a
    proposed action such as the establishment of an acceptable dose of
    a toxic chemical.

Cumulative exposure. The summation of exposures of an organism to a
    chemical over a period of time.

Degradation. Chemical or biological breakdown of a complex compond
    into simpler compounds.

Dermal exposure. Contact between a chemical and the skin.

Diffusion. The movement of suspended or dissolved particles from a
    more concentrated to a less concentrated region as a result of the
    random movement of individual particles; the process tends to
    distribute them uniformly throughout the available volume.

Dosage. The quantity of a chemical administered to an organism.

Dose. The actual quantity of a chemical to which an organism is exposed.
    (See absorbed dose)

Dose-response. A quantitative relationship between the dose of a
    chemical and an effect caused by the chemical.

Dose-response curve. A graphical presentation of the relationship
    between degree of exposure to a chemical (dose) and observed
    biological effect or response.

Dose-response evaluation. A component of risk assessment that describes
    the quantitative relationship between the amount of exposure to a
    substance and the extent of toxic injury or disease.

Dose-response relationship. The quantitative relationship between the
    amount of exposure to a substance and the extent of toxic injury
    produced.

DWEL. Drinking Water Equivalent Level -- estimated exposure (in mg/L)
    which is interpreted to be protetective for noncarcinogenic
    endpoints of toxicity over a lifetime of exposure. DWEL was
    developed for chemicals that have a significant carcinogenic
    potential (Group B). Provides risk manager with evaluation on
    non-cancer endpoints, but infers that carcinogenicity should be
    considered the toxic effect of greatest concern.

Endangerment assessment. A site-specific risk assessment of the actual
    or potential danger to human health or welfare and the environment
    from the release of hazardous substances or waste. The endangerment
    assessment document is prepared in support of enforcement actions
    under CERCLA or RCRA.

Endpoint. A biological effect used as an index of the effect of a
    chemical on an organism.

Epidemiologic study. Study of human populations to identify causes of
    disease. Such studies often compare the health status of a group
    of persons who have been exposed to a suspect agent with that of a
    comparable non-exposed group.

Exposure. Contact with a chemical or physical agent.

Exposure assessment. The determination or estimation (qualitative or
    quantitative) of the magnitude, frequency, duration, route, and
    extent (number of people) of exposure to a chemical.

Exposure coefficient. Term which combines information on the frequency, mode, and magnitude of contact with contaminated medium to yield a quantitative value of the amount of contaminated medium contacted per day.

Exposure level, chemical. The amount (concentration) of a chemical at the absorptive surfaces of an organism.

Exposure scenario. A set of conditions or assumptions about sources, exposure pathways, concentrations of toxic chemicals and populations (numbers, characteristics and habits) which aid the investigator in evaluating and quantifying exposure in a given situation.

Extrapolation. Estimation of unknown values by extending or projecting from known values.

Gavage. Type of exposure in which a substance is administered to an animal through a stomach tube.

Gram. 1/454 of a pound.

Half-life. The length of time required for the mass, concentration, or activity of a chemical or physical agent to be reduced by one-half.

Hazard evaluation. A component of risk assessment that involves gathering and evaluating data on the types of health injury or disease (e.g., cancer) that may be produced by a chemical and on the conditions of exposure under which injury or disease is produced.

Hematopoiesis. The production of blood and blood cells; hemopoiesis.

Hepatic. Pertaining to the liver.

Hepatoma. A malignant tumor occurring in the liver.

High-to-low-dose extrapolation. The process of prediction of low exposure risks to rodents from the measured high exposure-high risk data.

Histology. The study of the structure of cells and tissues; usually involves microscopic examination of tissue slices.

Human equivalent dose. A dose which, when administered to humans, produces an effect equal to that produced by a dose in animals.

Human exposure evaluation. A component of risk assessment that involves describing the nature and size of the population exposed to a substance and the magnitude and duration of their exposure. The evaluation could concern past exposures, current exposures, or anticipated exposures.

Human health risk. The likelihood (or probability) that a given exposure or series of exposures may have or will damage the health of individuals experiencing the exposures.

Incidence of tumors. Percentage of animals with tumors.

Ingestion. Type of exposure through the mouth.

Inhalation. Type of exposure through the lungs.

Integrated exposure assessment. A summation over time, in all media, of the magnitude of exposure to a toxic chemical.

Interspecies extrapolation model. Model used to extrapolate from results observed in laboratory animals to humans.

In vitro studies. Studies of chemical effects conducted in tissues, cells or subcellular extracts from an organism (i.e., not in the living organism).

In vivo studies. Studies of chemical effects conducted in intact living organisms.

Irreversible effect. Effect characterized by the inability of the body to partially or fully repair injury caused by a toxic agent.

Latency. Time from the first exposure to a chemical until the appearance of a toxic effect.

LC_{50}. The concentration of a chemical in air or water which is expected to cause death in 50 percent of test animals living in that air or water.

LD_{50}. The dose of a chemical taken by mouth or absorbed by the skin which is expected to cause death in 50 percent of the test animals so treated.

Lesion. A pathological or traumatic discontinuity of tissue or loss of function of a part.

Lethal. Deadly; fatal.

Lifetime exposure. Total amount of exposure to a substance that a human would receive in a lifetime (usually assumed to be seventy years).

Linearized multistage model. Derivation of the multistage model, where the data are assumed to be linear at low doses.

LOAEL. Lowest-Observed-Adverse-Effect Level; the lowest dose in an experiment which produced an observable adverse effect.

Malignant. Very dangerous or virulent, causing or likely to cause
        death.

Margin of safety (MOS). Maximum amount of exposure producing no
        measurable effect in animals (or studied humans) divided by the
        actual amount of human exposure in a population.

Mathematical model. Model used during risk assessment to perform
        extrapolations.

Metabolism. The sum of the chemical reactions occurring within a cell
        or a whole organism; includes the energy-releasing breakdown of
        molecules (catabolism) and the synthesis of new molecules (anabolism).

Metabolite. Any product of metabolism, especially a transformed chemical.

Metastatic. Pertaining to the transfer of disease from one organ or
        part to another not directly connected with it.

Microgram (ug). One-millionth of a gram (3.5 x 10^{-8} oz. = 0.000000035 oz.).

Milligram (mg). One-thousandth of a gram (3.5 x 10^{-8} oz. = 0.000035 oz.).

Modeling. Use of mathematical equations to simulate and predict real
        events and processes.

Monitoring. Measuring concentrations of substances in environmental
        media or in human or other biological tissues.

Mortality. Death.

MOS. See Margin of safety.

MTD. Maximum tolerated dose, the dose that an animal species can
        tolerate for a major portion of its lifetime without significant
        impairment or toxic effect other than carcinogenicity.

Multistage model. Mathematical model based on the multistage theory of
        the carcinogenic process, which yields risk estimates either equal
        to or less than the one-hit model.

Mutagen. An agent that causes a permanent genetic change in a cell
        other than that which occurs during normal genetic recombination.

Mutagenicity. The capacity of a chemical or physical agent to cause
        permanent alteration of the genetic material within living cells.

Necrosis. Death of cells or tissue.

Neoplasm. An abnormal growth or tissue, as a tumor.

Neurotoxicity. Exerting a destructive or poisonous effect on nerve
        tissue.

NOAEL. No-Observed-Adverse-Effect Level; the highest dose in an experiment which did not produce an observable adverse effect.

NOEL. No-Observed-Effect Level; dose level at which no effects are noted.

NTP. National Toxicology Program.

Oncology. Study of cancer.

One-hit model. Mathematical model 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, eventually leading to a tumor.

Oral. Of the mouth; through or by the mouth.

Pathogen. Any disease-causing agent, usually applied to living agents.

Pathology. The study of disease.

Permissible dose. The dose of a chemical that may be received by an individual without the expectation of a significantly harmful result.

Pharmacokinetics. The dynamic behavior of chemicals inside biological systems; it includes the processes of uptake, distribution, metabolism, and excretion.

Population at risk. A population subgroup that is more likely to be exposed to a chemical, or is more sensitive to a chemical, than is the general population.

Potency. Amount of material necessary to produce a given level of a deleterious effect.

Potentiation. The effect of one chemical to increase the effect of another chemical.

ppb. Parts per billion.

ppm. Parts per million.

Prevalence study. An epidemiological study which examines the relationships between diseases and exposures as they exist in a defined population at a particular point in time.

Prospective study. An epidemiological study which examines the development of disease in a group of persons determined to be presently free of the disease.

Qualitative. Descriptive of kind, type or direction, as opposed to size, magnitude or degree.

Quantitative. Descriptive of size, magnitude or degree.

Receptor. (1) In biochemistry: a specialized molecule in a cell that binds a specific chemical with high specificity and high affinity; (2) In exposure assessment: an organism that receives, may receive, or has received environmental exposure to a chemical.

Renal. Pertaining to the kidney.

Reservoir. A tissue in an organism or a place in the environment where a chemical accumulates, from which it may be released at a later time.

Retrospective study. An epidemiological study which compares diseased persons with non-diseased persons and works back in time to determine exposures.

Reversible effect. An effect which is not permanent, especially adverse effects which diminish when exposure to a toxic chemical is ceased.

RfD. Reference dose; the daily exposure level which, during an entire lifetime of a human, appears to be without appreciable risk on the basis of all facts known at the time. (Synonymous with ADI)

Risk. The potential for realization of unwanted adverse consequences or events.

Risk assessment. A qualitative or quantitative evaluation of the environmental and/or health risk resulting from exposure to a chemical or physical agent (pollutant); combines exposure assessment results with toxicity assessment results to estimate risk.

Risk characterization. Final component of risk assessment that involves integration of the data and analysis involved in hazard evaluation, dose-response evaluation, and human exposure evaluation to determine the likelihood that humans will experience any of the various forms of toxicity associated with a substance.

Risk estimate. A description of the probability that organisms exposed to a specified dose of chemical will develop an adverse response (e.g., cancer).

Risk factor. Characteristic (e.g., race, sex, age, obesity) or variable (e.g., smoking, occupational exposure level) associated with increased probability of a toxic effect.

Risk management. Decisions about whether an assessed risk is sufficiently high to present a public health concern and about the appropriate means for control of a risk judged to be significant.

Risk specific dose. The dose associated with a specified risk level.

Route of exposure. The avenue by which a chemical comes into contact
    with an organism (e.g., inhalation, ingestion, dermal contact,
    injection).

Safe. Condition of exposure under which there is a "practical certainty"
    that no harm will result in exposed individuals.

Sink. A place in the environment where a compound or material collects
    (see reservoir).

Sorption. a surface phenomenon which may be either absorption or
    adsorption, or a combination of the two; often used when the
    specific mechanism is not known.

Stochastic. Based on the assumption that the actions of a chemical
    substance results from probabilistic events.

Stratification. (1) The division of a population into subpopulations
    for sampling purposes; (2) the separation of environmental media
    into layers, as in lakes.

Subchronic. Of intermediate duration, usually used to describe studies
    or levels of exposure between five and 90 days.

Synergism. An interaction of two or more chemicals that results in
    an effect that is greater than the sum of their effects taken
    independently.

Systemic. Relating to whole body, rather than its individual parts.

Systemic effects. Effects observed at sites distant from the entry
    point of a chemical due to its absorption and distribution into
    the body.

Teratogenesis. The induction of structural or functional development
    abnormalities by exogenous factors acting during gestation;
    interference with normal embryonic development.

Teratogenicity. The capacity of a physical or chemical agent to cause
    non-hereditary congenital malformations (birth defects) in offspring.

Therapeutic Index. The ratio of the dose required to produce toxic or
    lethal effect to dose required to produce non-adverse or therapeutic
    response.

Threshold. The lowest dose of a chemical at which a specified measurable
    effect is observed and below which it is not observed.

Time-Weighted Average. The average value of a parameter (e.g., concen-
    tration of a chemical in air) that varies over time.

Tissue. A group of similar cells.

Toxicant. A harmful substance or agent that may injure an exposed organism.

Toxicity. The quality or degree of being poisonous or harmful to plant, animal or human life.

Toxicity assessment. Characterization of the toxicological properties and effects of a chemical, including all aspects of its absorption, metabolism, excretion and mechanism of action, with special emphasis on establishment of dose-response characteristics.

Transformation. Acquisition by a cell of the property of uncontrolled growth.

Tumor incidence. Fraction of animals having a tumor of a certain type.

Uncertainty factor. A number (equal to or greater than one) used to divide NOAEL or LOAEL values derived from measurements in animals or small groups of humans, in order to estimate a NOAEL value for the whole human population.

Unit cancer risk. Estimate of the lifetime risk caused by each unit of exposure in the low exposure region.

Upper bound estimate. Estimate not likely to be lower than the true risk.

Volatile. Readily vaporizable at a relatively low temperature.

B. TOXICOLOGICAL APPROACHES FOR DEVELOPING
NATIONAL DRINKING WATER REGULATIONS AND HEALTH ADVISORIES

by Edward V. Ohanian, Ph.D.
Chief, Health Effects Branch
Office of Drinking Water (WH-550D)
Washington, D.C.

Safe Drinking Water Act Requirements

° PUBLISH PRIMARY DRINKING WATER REGULATIONS

- Specify contaminants which "in the judgment of the Administrator, may have any adverse effect on the health of persons"

- Set for each contaminant either (a) MCL or (b) treatment technique

- Specify monitoring/reporting requirements and public notification

PRIMARY REGULATIONS

° Maximum Contaminant Level Goals (MCLGs)

- Health goal: non-enforceable

- Set at a level at which "no known or anticipated adverse effect on the health of persons occur and which allows an adequate margin of safety"

- House Report no. 93-1185: set MCLGs for carcinogens at zero

° Maximum Contaminant Levels (MCLs)

- Enforceable standards

- Set as close to MCLGs as feasible

SDWA AMENDMENTS -- PRIMARY DRINKING WATER REGULATIONS

° RMCL becomes MCLG (MCL Goals)

° Distinction between Interim and Revised Regulation deleted

° Requires EPA to propose and promulgate MCLGs and MCLs simultaneously

° NAS study deleted and replaced by requirement to consult with EPA Science Advisory Board

° Requires EPA to set regulations requiring public water systems to monitor for unregulated contaminants

° Requires EPA to prepare a Report to Congress on comparative health risks of raw water contamination versus contamination by treatment chemicals (e.g., disinfection by-products)

° Prohibits use of lead pipes, solder and flux

SDWA AMENDMENTS -- PRIMARY DRINKING WATER REGULATIONS - cont'd

SDWA requires EPA to:

° List 25 contaminants by January 1, 1988, for which MCLs would be set within 36 months

° Repeat every 3 years

° Establish Advisory Group to develop list

    - Include NTP and various EPA program offices

    - List must consider Section 101 CERCLA and registered pesticides

SDWA requires EPA to set regulations for 83 contaminants in two ANPRMs

° 9 MCLs in 12 months

° 40 MCLs in 24 months

° 34 MCLs in 36 months

MCLs REQUIRED UNDER SDWA AMENDMENTS

Volatile Organic Chemicals

Trichloroethylene	Vinyl chloride	Trichlorobenzene(s)
Tetrachloroethylene	Methylene chloride	1,1-Dichloroethylene
Carbon tetrachloride	Benzene	trans-1,2-Dichloroethylene
1,1,1-Trichloroethane	Chlorobenzene	cis-1,2-Dichloroethylene
1,2-Dichloroethane	Dichlorobenzene(s)	

Microbiology and Turbidity

Total coliforms	Giardia lamblia	Standard plate count
Turbidity	Viruses	Legionella

Inorganics

Arsenic	Mercury	Aluminum	Copper	Thallium
Barium	Nitrate	Antimony	Vanadium	Beryllium
Cadmium	Selenium	Molybdenum	Sodium	Cyanide
Chromium	Silver	Asbestos	Nickel	
Lead	Fluoride	Sulfate	Zinc	

MCLs REQUIRED UNDER SDWA AMENDMENTS (Continued)

Organics

Endrin	Carbofuran	Phthalates
Lindane	Alachlor	Acrylamide
Methoxychlor	Epichlorohydrin	Dibromochloropropane (DBCP)
Toxaphene	Toluene	1,2-Dichloropropane
2,4-D	Adipates	Pentachlorophenol
2,4,5-TP	2,3,7,8-TCDD (Dioxin)	Picloram
Aldicarb	1,1,2-Trichloroethane	Dinoseb
Chlordane	Vydate	Ethylene dibromide
Dalapon	Simazine	Dibromomethane
Diquat	PAHs	Xylene
Endothall	PCBs	Hexachlorocyclopentadiene
Glyphosate	Atrazine	

Radionuclides

Radium 226 and 228   Uranium
Beta particle and   Gross alpha particle activity
  photon radioactivity   Radon

ENVIRONMENTAL REGULATIONS

- Risk Assessment

- Risk Management

- Risk Communication

REGULATORY DEVELOPMENT

Occurrence   Analytical Methods
    +   +
Human Exposure
    +
Health Effects   Technology and Costs
    +   +
Risk Assessment   Economic Impact
    | +
    | Regulatory Impact
    ↓   ↓
  MCLG   MCL
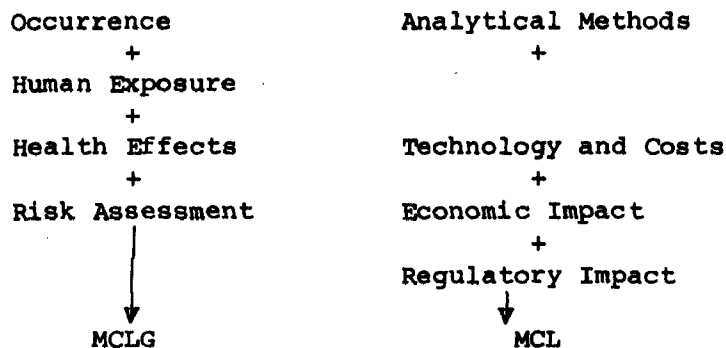
OBJECTIVES OF CRITERIA DOCUMENTS

° Establish core information base on health effects of chemicals in drinking water

° Compile and evaluate data for Maximum Contaminant Level Goals (MCLGs) and provide health effects basis for Maximum Contaminant Levels (MCLs)

° Provide health effects basis for health advisory values

DATA REVIEW AND EVALUATION

Members of the Office of Drinking Water's
Toxicology Review Panel (TRP)

Charles Abernathy, Ph.D.
Larry Anderson, Ph.D.
Kenneth Bailey, Ph.D., D.A.B.T.
Robert Cantilli, M.S.
Krishan Khanna, Ph.D.
Amal Mahfouz, Ph.D.
William Marcus, Ph.D., D.A.B.T.
Bruce Mintz, B.S.
James Murphy, Ph.D., D.A.B.T.
Edward Ohanian, Ph.D.
Jennifer Orme, M.S.
Yogendra Patel, Ph.D.

CRITERIA DOCUMENT CONTENTS

      I. Summary
     II. Physical and Chemical Properties
    III. Toxicokinetics
     IV. Human Exposure
      V. Health Effects in Animals
     VI. Health Effects in Humans
    VII. Mechanism of Toxicity
   VIII. Quantification of Toxicological Effects (QTE)
     IX. References

CONTENT OF QUANTIFICATION OF TOXICOLOGICAL EFFECTS

° Noncarcinogenic Effects
  - Selection of Key Studies
  - Selection of Uncertainty Factors
  - One-Day Health Advisory
  - Ten-Day Health Advisory
  - Longer-Term Health Advisory
  - Lifetime Health Advisory; Drinking
    Water Equivalent Level (DWEL)

° Carcinogenic Effects (CAG Cancer
  Risk Estimates

° Comparison with Existing
  Guidelines and Standards

° Special Considerations
  - High Risk Populations
  - Interactions
  - Beneficial Effects
  - Other Factors

NOAEL = No-observed-adverse-effect level

LOAEL = Lowest-observed-adverse-effect level

MCLGs: NON-CARCINOGENS

° 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% drinking water contribution

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

° Determine MCLG in mg/L

MCLG = (DWEL) (% drinking water contribution)*

*10% inorganics/20% organics

NAS/ODW GUIDELINES FOR APPLYING UNCERTAINTY FACTORS

° An uncertainty factor of 10 is used when good acute or chronic human exposure data are available and supported by acute or chronic toxicity data in other species.

° An uncertainty factor of 100 is used when good acute or chronic toxicity data identifying NOAEL are available for one or more species, but human data are not available.

° An uncertainty factor of 1,000 is used when limited or incomplete acute or chronic toxicity data in all species are available or when the acute or chronic toxicity data identify a LOAEL (but not NOAEL) for one or more species, but human data are not available.

° An intermediate uncertainty factor between 1 and 10 is used, according to scientific judgment.

APPLICATION OF UNCERTAINTY FACTOR REQUIRING "BEST SCIENTIFIC JUDGEMENT"

° Quality of toxicology data

° Severity of effect

° Duration/route of exposure

° Beneficial effect(s)

PREFERRED DATA FOR DWEL DEVELOPMENT

° Duration of Exposure
  - Chronic
  - Subchronic

° Route of Exposure
  - Oral: drinking water,
    gavage diet
  - Inhalation
  - Subcutaneous or intraperitoneal

° Test Species
  - Human
  - Appropriate animal model
  - Most sensitive species

° Dose-Response Relationship
  - NOAEL and LOAEL
  - LOAEL

° End-Point of Toxicity
  - Biochemical/patho-
    physiological changes
  - Body/organ weight changes
  - Mortality

IARC* CLASSIFICATION OF CARCINOGENS

Group	Evidence of Carcinogenicity
1	Suficient evidence of carcinogenicity to humans
2A	Limited evidence of carcinogenicity to humans
2B	Insufficient evidence of carcinogenicity to humans and sufficient evidence of carcinogenicity to animals
3	Available data cannot be classified as to its carcinogenicity to humans

* IARC - International Agency for Research on Cancer

EPA CLASSIFICATION OF CARCINOGENS

Group	Evidence of Carcinogenicity
A	Human carcinogen (sufficient evidence from epidemiological studies)
B	Probable human carcinogen
B_1	At least limited evidence of carcinogenicity to humans
B_2	Usually a combination of sufficient evidence in animals and inadequate data in humans
C	Possible human carcinogen (limited evidence of carcinogenicity in animals in the absence of human data)
D	Not classified (inadequate animal evidence of carcinogenicity)
E	No evidence of carcinogenicity for humans (no evidence for carcinogenicity in at least two adequate animal species or in both epidemiological and animal studies)

THREE-CATEGORY APPROACH FOR DEVELOPING MCLGs

Evidence of Carcinogenicity	Classification	MCLG
Strong	EPA Group A or B IARC Group 1, 2A or 2B	0
Equivocal	EPA Group C IARC Group 3	(a) RfD approach with additional safety factor, or (b) 10^{-5} to 10^{-6} cancer risk range
Inadequate or lacking	EPA Group D or E IARC Group 3	RfD approach

RISK ASSESSMENT CONCERNS

Science of Toxicology <--------> Art of Toxicology
FACT   PREDICTION

carcinogenic in animals   carcinogenic in humans
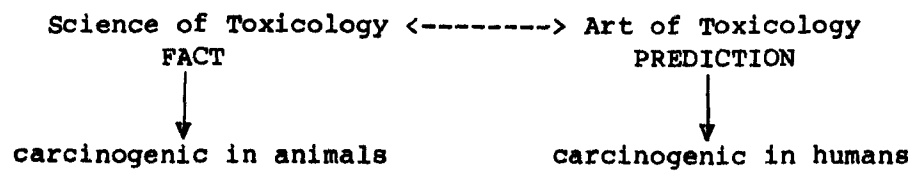
ODW REGULATORY HEALTH EFFECTS CRITERIA DOCUMENT (CD) DEVELOPMENT PROCESS

Time (months)	Regulatory Process	CD Development Process
0	Federal Register Notice ANPRM	Chemical Identification
6	Public Comment Period Public Meeting Public Workshop	Rough Draft CD * ODW Review
8		Rough External Draft Review CD ODW/ECAO** Review Expert Review (as needed)
12		External Review Draft CD ODW/ECAO** Review External Peer Review Agency Reivew
24	FR Notice MCLG/MCL Proposal	← Technical Support Document ← Final Draft CD
	Public Comment Period Public Meeting (s)	Public Comments ODW/ECAO** Review Agency Review
36	FR Notice MCLG/ MCL Promulgation	← Technical Support Document ← Final CD

*   Not applied to CDs prepared by ECAO/OHEA
** CDs prepared by ECAO/OHEA

C. EPA's HEALTH ADVISORY PROGRAM

Health Effects Branch
Criteria and Standards Division
Office of Drinking Water
U.S. Environmental Protection Agency

The Office of Drinking Water's non-regulatory Health Advisory Program provides information on health effects, analytical methodology and treatment technology that will be useful in dealing with contamination of drinking water. Health Advisories also describe concentrations of contaminants in drinking water at which adverse effects would not be anticipated to occur. A margin of safety is included to protect sensitive members of the population.

Health Advisories are not legally enforceable Federal standards. They are subject to change as new and better information becomes available. The Advisories are offered as technical guidance to assist Federal, State and local officials responsible for protection of the public health.

The Health Advisory numbers are developed from data describing non-carcinogenic endpoints of toxicity. They do not incorporate quantitatively any potential carcinogenic risk from such exposure. For those chemicals that are known or probable human carcinogens according to the proposed Agency classification scheme, non-zero One-day, Ten-day and Longer-term Health Advisories may be derived, with attendant caveats. Health Advisories for lifetime exposures may not be recommended. Projected excess lifetime cancer risks are provided to give an estimate of the concentrations of the contaminants at which a carcinogenic risk to humans may be posed. These hypothetical estimates usually are presented as upper 95% confidence limits derived from the linearized multistage model considered to be unlikely to underestimate the probable true risk.

When an Office of Drinking Water draft Health Effects Criteria Document is available, the Health Advisory is based upon information presented in the Criteria Document. The Health Advisory and Criteria Document formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization of a specific chemical should consult the Criteria Document for that chemical. Criteria Documents and Health Advisories are available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Public Water Supply Branch or Drinking Water Branch), or, for a fee, from the National Technical Information Service(NTIS),U.S. department of Commerce, 5285 Port Royal Road, Springfield, VA. The toll free number is (800) 336-4700; in the Washington DC area call (703) 487-4650. The NTIS document access number for ordering all 52 Health Advisories is PB 86-118338/AS. For additional information on the Health Advisory Program, please contact: Edward V. Ohanian, Ph.D., Chief, Health Effects Branch, Office of Drinking Water (WH-550D), U.S. EPA, 401 M. St.,S.W., Washington, DC 20460; Tel: (202) 382-7571.

ELEMENTS OF THE OFFICE OF DRINKING WATER'S HEALTH ADVISORY PROGRAM

° Establish comprehensive Health Advisories Registry (Computer-based)

° Prepare revised Health Advisories for about 50 contaminants

° Develop new Health Advisories for about 60 National Pesticide Survey(NPS) analytes

° Develop new Health Advisories for about 50 unregulated volatile synthetic organic chemicals(SOCs) under Section 1445

° Institute new preocedures to assure timely responses to emergency situations and requests for information

° Establish cooperative program between EPA and the Department of the Army on (Health Advisory development for) munitions chemicals in drinking water

° Initiate information-sharing and toxicological support program between EPA and States   (FSTRAC)

° Conduct 3-day Workshop for Users of Health Advisories and other water-related numbers on Philosophy/Methodology/Application in Risk Assessment/Risk Management Decision-making at all levels of government   (PIP)

WHAT ARE HEALTH ADVISORIES?

° Health Advisories are not legally enforceable Federal standards. They are subject to change as new and better information becomes available.

° Health Advisories describe concentrations of contaminants in drinking water at which adverse noncarcinogenic effects would not be anticipated to occur following 1-day, 10-day, longer-term or lifetime exposure

° Health Advisories are developed from data describing noncarcinogenic end-points to toxicity

° Health Advisories include carcinogenic potency factors and/or drinking water concentrations estimated to represent excess lifetime cancer risks over the range of 10^{-5} to 10^{-6} for:

   - All substances classified in Groups A and B
   - Some substances classified in Group C
   - No substances classified in Groups D and E

ODW HEALTH ADVISORY (HA) CONTENT

   I. General Introduction

   II. General Information and Properties
      ° Synonyms
      ° Uses
      ° Properties
      ° Sources of Exposure
      ° Environmental Fate

III. Pharmacokinetics
   ° Absorption
   ° Distribution
   ° Biotransformation
   ° Excretion

IV. Health Effects
   ° Humans
   ° Animals
       - Short-term Exposure
       - Longer-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

ASSUMPTIONS

Protected individual -- One-day HA: 10 kg child
                        Ten-day HA: 10 kg child
                        Longer-term HA: 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 liter
                        70 kg adult: 2 liters

Relative Source Contribution

                        In absence of chemical-specific data:
                        20% for organics
                        10% for inorganics

PREFERRED DATA FOR HA DEVELOPMENT

   ° Duration of Exposure: One-day HA: One to five (successive) daily doses
                             Ten-day HA: Seven to 14 (successive) daily doses
                             Longer-term HA: Subchronic (90 day) to one year
                             Lifetime HA: Chronic or subchronic (with an added
                                                       uncertainty factor)
   ° Route of Administration:
                             Oral: drinking water, gavage, diet, inhalation,
                             Subcutaneous or intraperitoneal (on a caseby-case
                             basis)

° Test Species: Human
                     Appropriate animal model
                     Most sensitive species

HEALTH ADVISORY (HA) CALCULATION

$$\frac{(\text{NOAEL or LOAEL in mg/kg/day}) \ (\text{BW in kg})}{(\text{UF(s)}) \ (\underline{\quad} \ \text{L/day})} = \text{mg/L}$$

Where:

NOAEL   = No Observed Adverse Effect Level
LOAEL   = Lowest Observed Adverse Effect Level
BW   = Body Weight of Protected Individual (10 kg or 70 kg)
UF(s)   = Uncertainty Factors
___ L/day = Daily Water Consumption (1 or 2 L/day)

DRINKING WATER EQUIVALENT LEVEL (DWEL)

° Definition:

   Estimated exposure (in mg/L or ug/L) which is interpreted to be protective
   for non-carcinogenic end-points of toxicity over a lifetime of exposure

° Application:

   - Developed for chemicals which have significant carcinogenic potential
     (Group B)

   - Provides risk manager with evaluation on non-cancer end-points, but infers
     that carcinogenicity should be considered the toxic effect of greatest concern

HEALTH ADVISORIES FOR Synthetic Organic Chemicals (SOCs), Volatile Organic Chemicals(SOCs), Inorganic Chemicals (IOCs) and MICROBIALS

Acrylamide	cis-1,2-Dichloroethylene	Methoxychlor
Alachlor	trans-1,2-Dichloroethylene	Methyl Ethyl Ketone
Aldicarb	Dichloromethane	Nickel
Arsenic	Dichloropropane	Nitrate/Nitrite
Barium	p-Dioxane	Oxamyl
Benzene	Dioxin	PCBs
Cadmium	EDB	Pentachlorophenol
Carbofuran	Endrin	Styrene
Carbon Tetrachloride	Epichlorohydrin	Tetrachloroethylene
Chlordane	Ethylbenzene	Toluene
Chlorobenzene	Ethylene Glycol	Toxaphene
Chromium	Heptachlor	2,4,5-TP
Cyanide	Hexachlorobenzene	1,1,1-Trichloroethane
2,4-D	n-Hexane	Trichloroethylene
DBCP	Lead	Vinyl Chloride
m/o-Dichlorobenzene	Lindane	Xylenes
1,2-Dichloroethane	Mercury	Legionella
1,1-Dichloroethylene		

PESTICIDE MONITORING SURVEY

° Joint ODW & OPP survey

° ODW's Objectives - Occurrence of pesticides in drinking water
  OPP's Objectives - Migration of pesticides from legal usage

° Complex survey
  - Sampling based upon pesticide usage and hydrogeology
  - Sampling weighted towards areas of probable occurrence
  - Approximately 1500 wells will be sampled

° Estimated cost: $5 million

° Estimated Schedule:
        FY85-86 - Identify chemicals and analytical methods
        FY85-86 - Select hydrogeology scheme
        FY86   - Finalize sampling technique
        FY86   - Pilot sampling
        FY87-89 - Full sampling
        FY89-90 - Final report

TENTATIVE LIST OF ANALYTES FOR THE NATIONAL PESTICIDE SURVEY

Acifluorfen	Diazinon	Methomyl
Alachlor	Dicamba	Mthyl Parathion
Aldicarb	2,4-D	Metolachlor
Ametryn	1,2-Dichloropropane	Metribuzin
Ammonium Sulfamate	Dieldrin	Oxamyl
Atrazine	Dimethrin	Paraquat
Baygon	Dinoseb	PCP
Bentazon	Diphenamid	Picloram
Bromacil	Disulfoton	Prometone
Butylate	Diuron	Pronamide
Carbaryl	EDB	Propachlor
Carbofuran	ETU/EDBCs	Propazine
Carboxin	Endothall	Propham
Chloramben	Fenamiphos	Simazine
Chlordane	Fluometuron	Trifluralin
Chlorothalonil	Fonofos	2,4,5-T
Cyanazine	Glyphosate	2,4,5-TP
Cycloate	Hexazinone	Tebuthiuron
Dalapon	Maleic Hydrazide	Terbacil
DBCP	MCPA	Terbufos
DCPA/Dacthal		

Chloroform	Chloromethane
Bromodichloromethane	Bromomethane
Chlorodibromomethane	Bromochloromethane
Bromoform	1,2,3-Trichloropropane
trans-1,2-Dichloroethylene	1,2,3-Trichlorobenzene
Chlorobenzene	n-Propylbenzene
m-Dichlorobenzene	1,1,1,2-Tetrachloroethane
Dichloromethane	Chloroethane
cis-1,2-Dichloroethylene	1,1,2-Trichloroethane
o-Dichlorobenzene	Pentachloroethane
1,2,4-Trichlorobenzene	bis-2-Chloroisopropyl ether
Fluorotrichloromethane	sec-Dichloropropane
Dichlorodifluoromethane	1,2,4-Trimethylbenzene
Dibromomethane	n-Butylbenzene
1,2-Dibromo-3-chloropropane	Naphthalene
Toluene	Hexachlorobutadiene
p-Xylene	o-Chlorotoluene
o-Xylene	p-Chlorotoluene
m-Xylene	1,3,5-Trimethylbenzene
1,1-Dichloroethane	p-Cymene
1,2-Dichloropropane	1,1-Dichloropropane
1,1,2,2-Tetrachloroethane	iso-Propylbenzene
Ethylbenzene	tert-Butylbenzene
1,3-Dichloropropane	sec-Butylbenzene
Styrene	Bromobenzene

HEALTH ADVISORIES ON MUNITIONS CHEMICALS -MEMORANDUM OF UNDERSTANDING BETWEEN THE DEPARTMENT OF THE ARMY AND THE ENVIRONMENTAL PROTECTION AGENCY

RESPONSIBILITIES

Department of the Army

° Provide priority ranking of munitions compounds
° Provide central point of contact for coordination activities
° Disseminate agreement to affected Army subordinate commanders
° Provide relevant data from concerned Army activities
° Arrange visits by key EPA personnel to Army facilities
° Provide support to EPA as resources permit

Environmental Protection Agency

° Authorize personnel to work with Army to develop data bases
° Provide Health Advisories based on health effects* in a timely manner when data are available
° Define significant data deficiencies or problem areas
° Provide recommendations for future data base development
° Submit periodic progress reports

* Health Advisories do not address explosive, flammable, etc. hazards of munitions.

LIST OF CHEMICALS FOR WHICH TOXICITY PROFILES HAVE BEEN PREPARED FOR THE
DEPARTMENT OF THE ARMY

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

FEDERAL-STATE TOXICOLOGICAL RISK ASSESSMENT COMMITTEE (FSTRAC)

Description: Working Group composed of EPA and State experts in the areas of risk assessment/management for drinking water contaminants

Goals: Cooperation, consistency and information exchange

Activities: Peer review, methodology articulation, survey coordination and research

EPA PERFORMANCE IMPROVEMENT PROJECT (PIP) WORKSHOP ON ASSESSMENT AND MANAGEMENT OF DRINKING WATER CONTAMINATION

° Principles of pharmacokinetics risk asessment and carcinogenicity
° Understanding ODW Health Advisories
° Toxicology of inorganics, solvents and pesticides
° Drinking water treatment
° Treatment cost case study
° Risk assessment case study
° Risk communication
° Risk management case study

ODW HEALTH ADVISORY (HA) DEVELOPMENT PROCESS

Time
(months)

0

Chemical Identification

2

Rough Draft HA

ODW Review *

4

**Rough External Review
Draft HA**

ODW Review*
Expert Review (as needed)
Editorial Review

6

External Review / Draft HA

ODW Review
External Peer Review
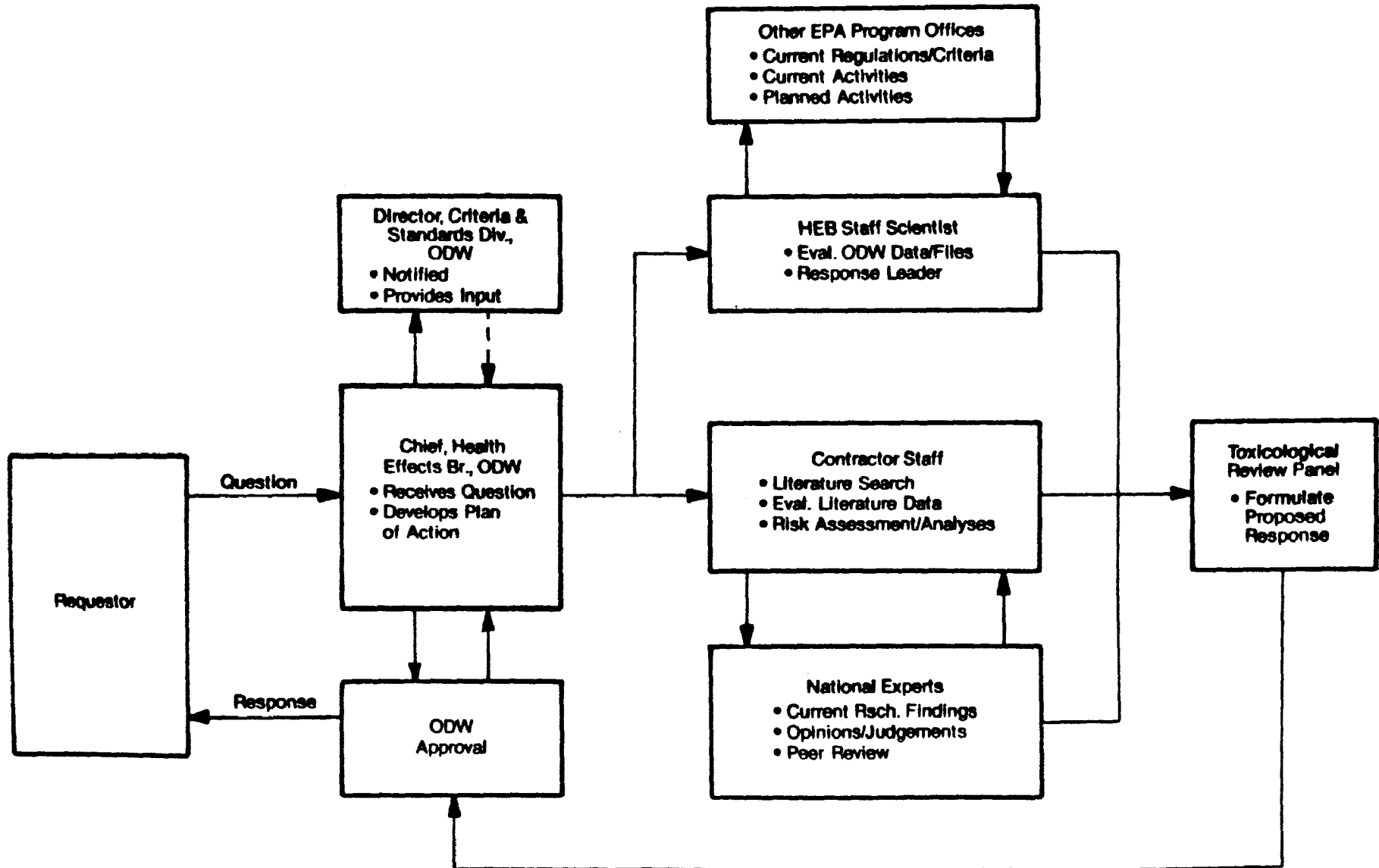(SAB/SAP Review)
Agency Review

9

Final Draft HA

Public Comments
ODW Review
Agency Review

12

FINAL HA

* CSD Toxicology Review Panel

ODW PROCESSING OF EMERGENCY RESPONSE REQUESTS

Other EPA Program Offices
- Current Regulations/Criteria
- Current Activities
- Planned Activities

Director, Criteria & Standards Div., ODW
- Notified
- Provides Input

HEB Staff Scientist
- Eval. ODW Data/Files
- Response Leader

Chief, Health Effects Br., ODW
- Receives Question
- Develops Plan of Action

Contractor Staff
- Literature Search
- Eval. Literature Data
- Risk Assessment/Analyses

Toxicological Review Panel
- Formulate Proposed Response

Requestor

Question

Response

ODW Approval

National Experts
- Current Rsch. Findings
- Opinions/Judgements
- Peer Review

ODW EMERGENCY RESPONSE NETWORK

QUESTIONS   ODW EVALUATIONS   RESPONSES

By:
- Letter (normal)

- Telephone (fast-response)

ODW
Health
Effects
Branch

HEB Staff Scientist
- Response Leader
- EPA Coordination

Contractor Support
- Contractor Staff
- National Experts

Formal:
- Letter

Informal/Interim:
- Telephone Call
- Conference Call

From:
- EPA Region
- State EPA/Health Dept.
- Local Government
- Water Treatment Fac.
- Others

PART II

RISK ASSESSMENT

A. Safety Evaluation/General Principles of Toxicology
B. Acute and Chronic Toxicity Tests
C. Use of Toxicity Data in Regulations
D. Absorption, Distribution, Excretion and Metabolism of Chemicals
E. Toxicology of Inorganics
F. Toxicology of Pesticides
G. Toxicology of Solvents and Vapors
H. Chemical Carcinogens
I. Principles of Risk Assessement
J. Assessing Risk/Introduction to Case Study Exercise
K. Risk Assessment Case Study of Drinking Water Contaminated by Vinyl Cloride

SAFETY EVALUATION
GENERAL PRINCIPLES OF TOXICOLOGY
CURTIS D. KLAASSEN, PH.D.

A.

I. GENERAL DEFINITIONS

   A. Toxicology: The study of the adverse effects of chemicals on living organisms.

   B. Toxicologist: Trained to examine the nature of these adverse effects and to assess the probability of their occurrence.

      1. Descriptive

      2. Mechanistic

      3. Regulatory

II. SPECTRUM OF UNDESIRED EFFECTS

   A. Side effects or undesirable

   B. Adverse, deleterious, or toxic

      1. Immediate versus delayed

      2. Reversible versus irreversible

      3. Local versus systemic

      4. Idiosyncratic – genetically determined abnormal reactivity but qualitatively similar

      5. Allergic or sensitization reactions

III. CLASSIFICATION OF TOXIC AGENTS

   A. Target organ

   B. Source

   C. Effects

   D. Physical state

   E. Labeling requirements

F. Chemistry

G. Toxicity Rating

H. Mechanism of action

IV. CHEMICAL EXPOSURE

A. Acute: single

B. Subacute: less than 1 month

C. Subchronic: 1-3 months

D. Chronic: more than 3 months

V. DOSE-RESPONSE
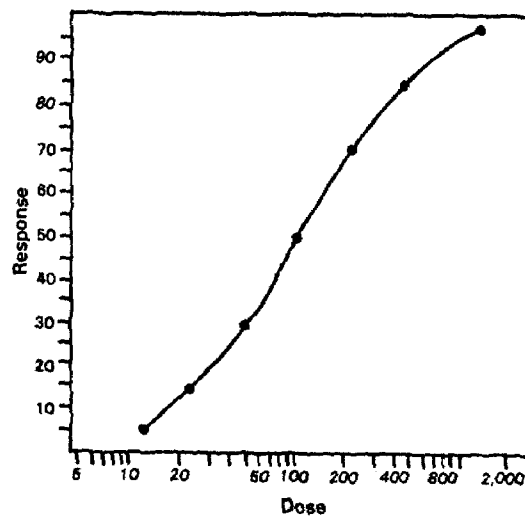
hypersusceptible   resistant

# VI. CONVERSION OF SIGMOID DOSE-RESPONSE CURVE TO STRAIGHT LINE
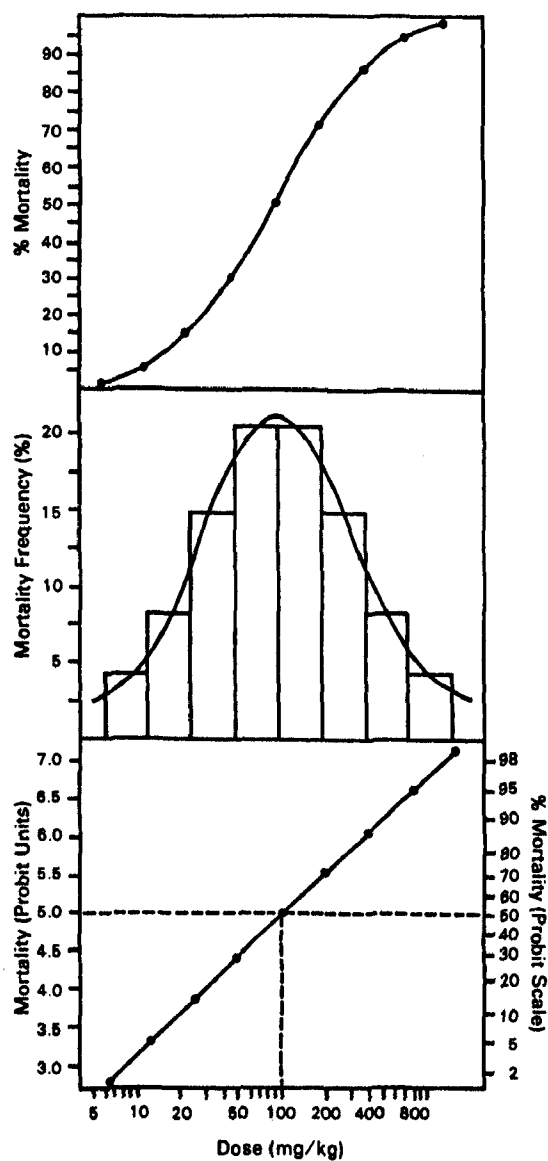
VII. POISON: Any Chemical Capable of Producing a Deleterious Response in a Biologic System, Seriously Injuring Function or Producing Death

"All Substances are Poisons; There is None which is Not a Poison. The Right Dose Differentiates a Poison and a Remedy." (Paracelsus 1493-1541)

VIII. CLASSIFICATION OF TOXICANTS

Probable Oral Lethal Dose for Humans

	LD50 (mg/kg)	Toxicity Rating
		practically nontoxic (above 15 g/kg)
Ethyl Alcohol	10,000	slightly toxic (5-15 g/kg)
Sodium chloride	4,000	moderately toxic (0.5-5 g/kg)
Phenobarbital	150	very toxic (50-500 mg/kg)
Parathion	7	extremely toxic (5-50 mg/kg)
Strychnine	2	super toxic (less 5 mg/kg)
Nicotine	1	
d-tubocurarine	0.05	
Tetradotoxin	0.01	
TCDD	0.001	
Botulinus toxin	0.00001	

IX. SLOPE OF THE DOSE-RESPONSE
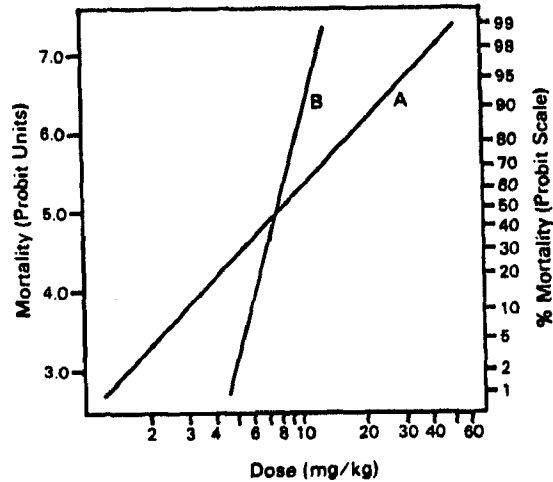
X. USE OF DOSE-RESPONSE FOR EFFECTS OTHER THAN DEATH
A. Liver injury
B. Cancer
C. Etc.
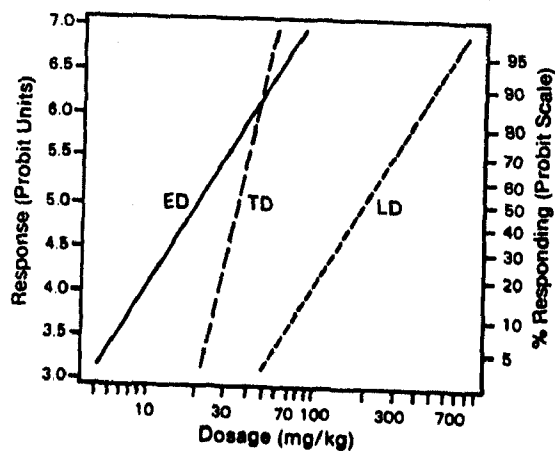
XI. THERAPEUTIC INDEX AND MARGIN OF SAFETY

A. Therapeutic index $= \dfrac{LD50}{ED50}$

B. Margin of safety $= \dfrac{LD1}{ED99}$

    1. If use for 1 month $= 10$

    2. If use for 6 months $= 100$

    3. If food additive $= 1000$

XII. CHEMICAL INTERACTIONS

A. Additive: $2 + 3 = 5$

B. Synergistic: $2 + 3 = 20$

C. Potentiation: $0 + 2 = 10$

D. Antagonism: $4 + 6 = 8$

                               $4 + (-4) = 0$

                               $4 + 0 = 1$

    1. Functional

    2. Chemical

    3. Dispositional

    4. Receptor

ACUTE AND CHRONIC TOXICITY TESTS
CURTIS D. KLAASSEN, PH.D.

I. TWO MAIN PRINCIPLES OF DESCRIPTIVE ANIMAL TOXICITY TESTS

A. Effects produced by a compound in laboratory animals, when properly qualified, are applicable to man.

B. Exposure of experimental animals to toxic agents in high doses is a necessary and valid method of discovering possible hazards in man (for 0.01% which is 20,000 people in 200 million, it requires 30,000 animals)

II. DESCRIPTIVE ANIMAL TOXICITY TESTS

A. Acute

1. Oral LD50 (gavage)

a. Often do a pilot range finding study first

(1) For small rodents inject 2 rats or 2 mice each with 0.5, 5, 50, 500 and 5000 mg/kg

(2) For dogs, use one dog and increase dose 10 fold each day until death – then give that dose to next dog

b. Typical protocol

(1) Often starve animals for 16 hrs before administration

(2) Usually administer constant concentration for various doses rather than a constant volume

(3) Observe the animals at 1, 2 and 4 hrs and daily for 14 days

(4) Usually calculated as number of deaths at 14 days after administration

(5) Body weight of animals at 14 days

(6) Minimal or no histopathology or clinical

chemistry except in the dog. Clinical chemistry often performed before administration and on days 2, 7 and 14

2. Acute dermal toxicity (LD50)

   a. Typical protocol

      (1) Albino rabbits

      (2) Area of application free of hair and abraided

      (3) If a solid, moistened with saline

      (4) Kept in contact for 24 hrs

      (5) Observe for 2 weeks

      (6) If no toxicity at 2 g/kg, no further testing necessary

3. Acute inhalation toxicity (LC50)

   a. Typical protocol

      (1) As above (under typical protocol for oral LD50)

      (2) 4 hr exposure

4. Primary eye irritation

   a. Typical protocol

      (1) Rabbits

      (2) Place liquid or solid (not moistened) in eye (0.1 ml of liquid or 100 mg of solid)

      (3) Other eye serves as control

      (4) In some animals flush eye, others don't

      (5) Grade and score eye irritation at 1, 2, 3, 4, 7 and every 3 days thereafter until toxicity subsides

5. Primary skin irritation

   a. Typical protocol

      (1) Rabbit

(2) Hair clipped

(3) 0.5 ml liquid or 0.5 g solid

(4) Covered by gauze and then plastic

(5) Chemical in contact with skin for 4 hrs

(6) Erythema and edema scored at 24 and 72 hrs after application

6. Skin sensitization (Guinea pigs)

a. Draize

b. Freunds complete adjuvant test (FCAT)

c. Guinea pig maximization

d. Split adjuvant

e. Beuhler occlusive

f. Open epicutaneous

B. Subacute

1. To determine dose levels for subchronic study

2. Typical protocol

a. 14 days

b. In rodents, 4 doses, 10 animals per sex per dose, for dogs, 3 doses, 3 dogs per sex per dose

c. Observe twice a day

d. Do clinical chemistry, histopathology, etc.

C. Subchronic

1. Typical protocol

a. 90 days (13 weeks)

b. At least 3 doses and controls

c. 2 species (15 rats of each sex per dose and 4 dogs of each sex per dose)

d. Route of intended use or exposure (usually diet)

2. Typical observations

a. Mortality

b. Body weight changes

c. Diet comsumption

d. Urinalysis (color, specific gravity, pH, albumin, sugar, leukocytes, erythrocytes, epithelial cells, casts, bacteria, crystals)

e. Hematology (RBC, WBC, platelets, differential)

f. Clinical chemistry (glucose, creatinine, BUN, uric acid, sodium, potassium, CO_2, chloride, calcium, phosphorus, cholesterol, triglycerides, bilirubin, SGOT, SGPT, lactate dehydrogenase, alkaline phosphatase, iron, total protein, albumin, globulin)

g. Gross and microscopic examination (brain, heart, liver, kidney, spleen, testes, thyroid, adrenal [and weigh the 8 aforementioned organs], aorta, bone, bone marrow-smears, gall bladder, esophagus, duodenum, jujunum, cecum, colon, lung, lymph node, sciatic nerve, parathyroid, pituitary, salivary gland, epididymis, prostate)

D. Chronic

1. Typical protocol

a. Duration depends on intended period of exposure in man. May be only 6 months, if to determine carcinogenic potential, then other average lifetime of species. 60 Animals per sex per dose often started to assure 30 rats survive. Otherwise similar to subchronic.

b. For dogs, often use 3 doses and 6 male and 6 female per dose. Typical duration is 12 months. Clinical chemistry performed on dogs before and at 1, 3, 6, 9 and 12 months after commencement of chemical administration.

2. Typical observations

a. Similar to subchronic

b. In dogs often do opthalmic examination every 6 months

E. Fertility and reproductive (Phase I)

1. Typical protocol

   a. Two or three doses (which produce no maternal toxicity)

   b. Male given 60-80 days and female 14 days prior to mating

   c. 25 rats per dose

2. Typical observations

   a. Percent pregnant

   b. Number of stillborn and live offspring

   c. Weight, growth, survival and general condition during first 3 weeks of life.

F. Teratogenic (Phase II)

1. Typical protocol

   a. Same doses as above

   b. Rats (25 per dose) and rabbits (20 per dose)

   c. Exposed on days 6-15

      (1) Day 0 in rabbit is day of mating

      (2) In rodents, day 0 is when vaginal plug or sperm in vaginal smear

   d. Fetuses removed by cesaerean section two or three days before normal parturition

      (1) Rat - day 20

      (2) Rabbit - day 29

2. Typical observations

   a. Number of implantations

   b. Number of dead and living fetuses

c. Fetuses weighed, measured and examined grossly

    d. Histological and skeletal examination

G. Perinatal and Postnatal (Phase III)

    1. Typical protocol

        a. 15 days of gestation throughout delivery and lactation

    2. Typical observations

        a. Similar to fertility study

H. Multigeneration reproduction study

    1. Typical protocol

        a. Rats

        b. F_0 generation given chemical from 40 days of age until breeding at day 140. F_1 thus exposed in utero and all their life including breeding and development of F_2 generation. F_0 are exposed about 160 days, F_1 about 270 days and F_2 about 60 days.

        c. 25 females

        d. 3 dose levels and control

        e. Gross necropsy and histopathology

            (1) F_1: Ten males and 25 females from each dose

            (2) F_1 and F_2: Five randomly selected weanlings of each sex of each dose and generation

I. Mutagenic

    1. Cytogenic analysis of bone marrow

    2. Dominant lethal

    3. Salmonella reverse mutation (Ames)

J. Other tests

    1. Toxicokinetics

    2. Antidotes

3. Wildlife

K. Typical costs of descriptive toxicity tests

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 tox tests

Reverse mutation assay (S.typhimurium)	1,000
Mammalian bone marrow cytogenetics (in vivo)	13,000
Micronucleus test	2,000
Dominant lethal in mice	8,500
Host mediated assay	4,400
Drosophila	12,500

Subchronic mouse study (190 days)	45,000
Rat oncogenecity	450,000
Mouse oncogenicity	300,000
Reproduction	200,000
Teratology (2 species)	45,000
Acute toxicity in fish (LC50)	1,250
Daphnia reproduction study	1,400
Algae growth inhibition	1,450

I. USE OF TOXICITY DATA IN REGULATIONS

A. If no carcinogenicity, teratogenicity, or mutagenicity use uncertainty factor

1. If prolonged ingestion studies in man $\dfrac{NOEL}{10}$

2. If chronic studies in animals $\dfrac{NOEL}{100}$

3. If only scanty results in animals $\dfrac{NOEL}{1000}$

B. Risk vs Safety

1. Risk: The probability that a substance will produce harm under specified conditions

2. Safety: The probability that harm will not occur under specified conditions

3. Estimated risks

   a. 1/4000: Automobile accident
   b. 1/2,000,000: Lightning

4. Acceptable risk

   a. People in U.S. $=$ 2.2 x 10^8
   b. Lifespan $=$ 80 years
   c. Acceptable risk $=$ 30 tumors per years
   $=$ 1 in 100,000
   $=$ 0.00001 or 10^{-5}
   $=$ 0.001%

5. VSD $=$ Virtually safe dose

6. Mathematics used in determining the dose that should give dose that will produce that acceptable risk
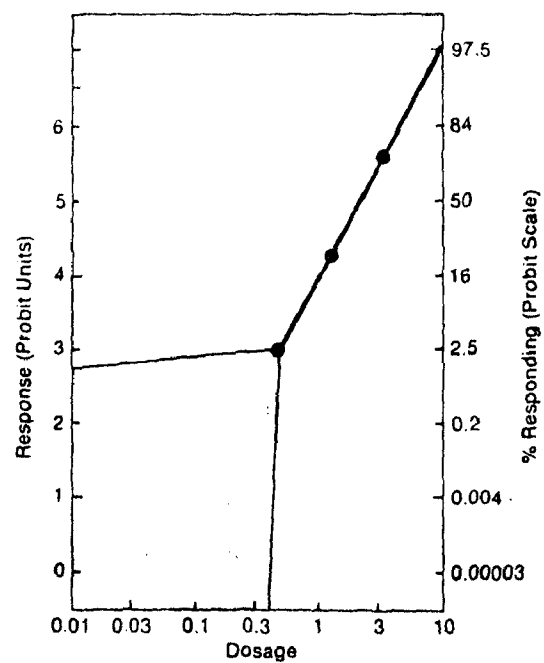
ABSORPTION, DISTRIBUTION, EXCRETION & METABOLISM
CURTIS D. KLAASSEN, PH.D.

I. MECHANISMS BY WHICH TOXICANTS PASS BODY MEMBRANES

A. Passive Transport

1. Simple diffusion

a. Of lipid soluble compounds

b. Nonionized chemicals are more lipid soluble

2. Filtration: when water flows in bulk across a porous membrane, any solute that is small enough to pass through the pores flows with it.

II. ABSORPTION OF TOXICANTS

A. Gastrointestinal tract

1. Lipid soluble compounds (nonionized) more readily absorbed than lipid insoluble compounds (water soluble, ionized)

2. Specialized transport systems – sugars, amino acids, pyrimidines, calcium and sodium

3. Almost everything is absorbed at least to a small extent

4. Effect of digestive fluids on chemicals

a. Snake venom

b. Nitrate to nitrite in newborns

5. Age – newborn has poor intestinal barrier

6. First pass – chemical can be extracted and/or biotransformed by intestine or liver before reaches systemic circulation

B. Lungs

1. Anatomically good for absorption

a. Large surface area (50–100 sq m)

b. Blood flow is high

c. Close to blood (10 um)

C. Skin

1. Is a relatively good barrier (many cells thick)

2. Absorption through follicles is rapid

3. Absorption trans dermally is quantitatively more important

4. Absorption by passive diffusion

5. Abrasion increases absorption

III. DISTRIBUTION OF TOXICANTS

A. Distribution to various organs dependent on

1. Blood flow through the organ

2. Ease it crosses cell membranes

3. Affinity of various tissues for the toxicant

B. Site of concentration in body is not necessarily the target organ of toxicity

C. Fat as a storage depot

D. Bone as a storage depot

E. Blood-brain barrier

F. Placenta barrier

IV. EXCRETION OF TOXICANTS

A. Route of excretion of toxicants

1. Urine

2. Bile

3. Air

4. Gastrointestinal tract

5. Cerebrospinal fluid

6. Milk

7. Saliva, sweat, tears, etc.

B. Mechanisms of excretion into urine

1. Glomerular filtration
   a. All toxicants with MW < 60,000

   b. If not bound to plasma proteins

2. Passive tubular diffusion

   a. If lipid soluble

3. Active secretion - carrier mediated

   a. Two separate carriers

      1) Organic acids - P-aminohippurate

      2) Organic bases - N-methylnicotinamide

C. Biliary excretion

   1. Mechanisms of excretion into bile

      a. Diffusion

      b. Carrier mediated transport

         1) Organic acid

         2) Organic base

         3) Organic neutral

   2. Enterohepatic circulation

D. Lung

   1. Important for substances that exist in gas phase at body temperature

   2. Mechanisms of elimination - diffusion

E. Gastrointestinal tract

   1. Sources of toxicants in feces

      a. Not completely absorbed

      b. Excreted into bile

      c. From respiratory tract and swallowed

      d. Excreted in saliva, pancreatic or gastric secretions

F. Milk

   1. Importance

      a. Toxic material may be passed from mother to nursing child

      b. Compounds may be passed from cows to humans

   2. Diffusion is the mechanism of transfer

      a. Ion trapping – pH is 6.5 – basic compounds may concentrate

      b. Lipid – 3.5% – DDT, PCB, PBB

G. Sweat and saliva

H. Half life – time it takes for one half of the chemical to be eliminated from the body

V. METABOLISM OR BIOTRANSFORMATION OF TOXICANTS

A. Purpose – make more water soluble

B. Result

   1. Detoxification

   2. Toxification

   3. No change

C. Two phases of biotransformation

   1. Phase I: oxidation, reduction, hydrolysis

   2. Phase II: conjungation or synthesis

D. Location: mainly liver, but all tissues can

E. Qualitative

   1. Phase I

      a. Cytochrome P-450 monooxygenase

      b. Example of the general type of oxidation reactions catalyzed by the cytochrome P-450-containing monooxygenases

         1) Aromatic hydroxylation

         2) Aliphatic hydroxylation $RCH_2CH_2CH_3 \rightarrow RCH_2CHOHCH_3$
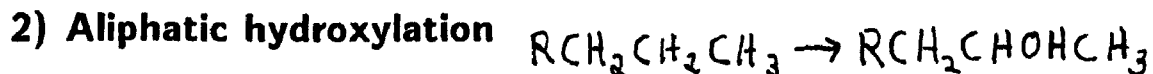
3) N, O and S-dealkylation $R-(\overset{H}{N}, O, S)-CH_3 \rightarrow R(NH_2, OH, SH)$

4) Epoxidation $R-CH=CHR' \rightarrow R-\overset{O}{CH-CH}-R'$

5) Desulfuration $R_1 R_2 \overset{S}{P}-X \rightarrow R_1 R_2 \overset{O}{P}-X + S$

6) Sulfoxidation $RSR_1 \rightarrow R-\overset{O}{S}-R_1$

7) N-hydroxylation $RNH-\overset{O}{C}-CH_3 \rightarrow R-NOH\overset{O}{C}CH_3$

c. **Non P-450**

1) **Amine oxidase - not P-450**

2) **Epoxide hydrolase (closely associated with P-450)**
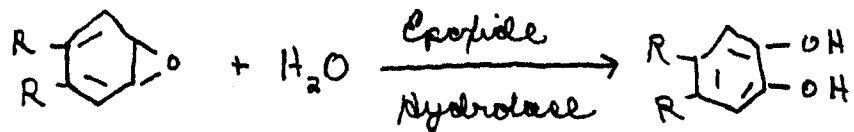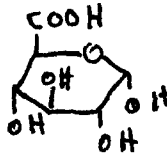

3) **Esterases and amidases**

$$CH_3\overset{O}{C}-OC_2H_5 \longrightarrow CH_3\overset{O}{C}OH + CH_3CH_2OH$$
$$ethyl\ acetate \qquad acetic\ acid \qquad ethanol$$
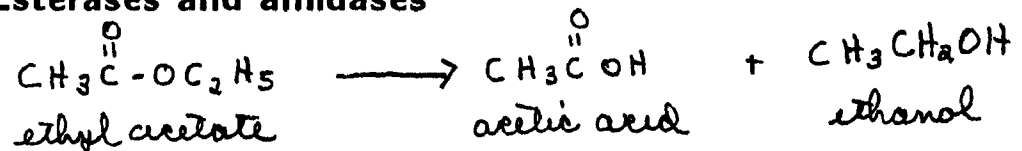
4) **Alcohol and aldehyde dehydrogenase**

$$CH_3CH_2OH + NAD^+ \longrightarrow CH_3\overset{O}{C}H \rightarrow CH_3\overset{O}{C}OH$$
$$acetaldehyde \quad acetate$$
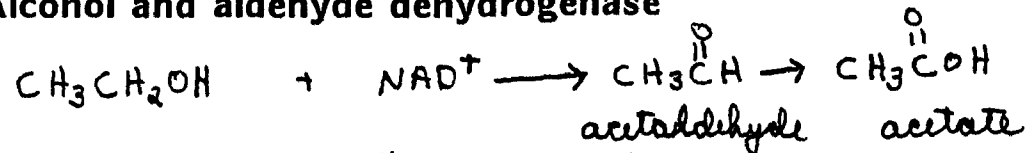
2. **Phase II - conjugation**

a. **Glucuronic acid**

b. **Glutathione S-transferase**

1) **Tripeptide (glycine, cysteine and glutamic acid)**

2) **Enzymatically take off by peptidases**

(1) **Glutamic acid**

(2) **Glycine**

3) **N-acetyl transferase**

4) **Then mercapturic acid**

c. **Sulfotransferase - sulfate**

d. Amino acid conjugates - glycine, glutamine, taurine

e. Methyl transferases

    1) Does not increase water solubility

f. N-acetyl transferases

    1) Decrease water solubility

    2) Pharmacogenetics

VI. QUANTITATIVE - FACTORS THAT AFFECT RATE OF BIOTRANSFORMATION

A. Species difference - quantitative and qualitative

B. Strain differences

C. Sex differences

D. Age

E. Enzyme induction

    1. Type

        a. Increase P-450, Phenobarb, DDT

        b. Increase P-448, 3-MC, PCB, TCDD

VII. THE MATHEMATICAL QUANTITATION OF ABSORPTION, DISTRIBUTION AND EXCRETION IS REFERRED TO AS

1. Pharmacokinetics

2. Toxicokinetics

TOXICOLOGY OF INORGANICS

CURTIS D. KLAASSEN, PH.D.

I. LEAD (0.020 MG/L)

  A. Sources

    1. Environment from tetraethyl lead in gasoline

    2. Old paint - pica (craving for unnatural food)

    3. Improperly lead-glazed earthenware - acid

    4. Occupational - smelters, storage-battery factories

    5. Moonshine

    6. Automobile battery casings - fuel

    7. Water distribution pipes and solder

  B. Absorption, Distribution and Excretion

    1. Absorption: 10% ingested absorbed

    2. Initial distribution: kidneys and liver

    3. Redistribution: 95% in bone (X-rays)

    4. Does not readily enter CNS except in children

    5. Excretion: laboratory animals in bile, humans in urine; since lead is in erythrocytes it is filtered slowly

    6. Excretion is limited

      a. Normal intake 0.3 mg/day

      b. Positive lead balance 0.6 mg/day - no toxicity in lifetime

      c. 2.5 mg/day - 4 yrs to toxic burden

      d. 3.5 mg/day - few months to toxicity

  C. Acute Lead Poisoning

    1. Rare

  D. Chronic Lead Poisoning (plumbism)

    1. Gastrointestinal effects

a. More common among adults

b. Referred to as lead colic

c. Often the symptoms for which patient seeks relief

d. Calcium gluconate for relief of pain

2. Neuromuscular Effects

a. Referred to as lead palsy

b. Wrist-drop and foot-drop

3. Central Nervous System Effects

a. Termed lead encephalopathy

b. Most serious manifestation of lead toxicity

c. More common in children

d. 25% mortality - 40% of survivors have neurological sequelae

4. Hematologic Effects

a. Basophilic stippling (RNA in RBC's) - seen in only 60% of cases among children and less in adults

b. Anemia

c. Heme synthesis: interference of heme synthesis resulting in porphyria

5. Renal Effects

a. Kidney injury

b. Cancer in laboratory animals (B2)

E. Diagnosis of Lead Poisoning

1. Symptomology

2. History of exposure

3. Blood - lead concentration

a. 10-40 ug/100 g blood: normal

b. 40-60 ug/100 g blood: decrease ALA dehydrase and slight increase in urinary ALA excretion

c. 60-80 ug/100 g blood: mild symptoms

            d. greater 80 ug/100 g: clear-cut symptoms

            e. 120 ug/100 g: encephalopathy

        4. X-rays of long bones

        5. ALA and coproporphyrin concentrations in urine

    F. Organic Lead Poisoning

        1. CNS: insomnia, nightmares, irritability, anxiety

        2. Car exhaust is organic

II. MERCURY (0.003 mg/L)

    A. Chemical Forms and Sources of Mercury

        1. Elemental mercury - mercury vapor

        2. Mercury salts

            a. Monovalent mercurous salts

                ex) Mercurous chloride or calomel:
                    skin cream, antiseptic, diuretic, cathartic

            b. Divalent mercuric salts

                ex) Mercuric nitrate: felt-hat industry "madhatter"

        3. Organomercurials

            a. Fungicides

                1) Huckleby family of Alamogordo, NM

                2) Iraq, 1972

            b. Fish

                1) Minamata Bay, Japan

                2) Tuna and Swordfish in USA

    B. Absorption, Biotransformation, Distribution and Excretion

        1. Elemental mercury

a. Orally - nontoxic

b. Lung - readily absorbed, oxidized by RBC to divalent mercuric cation

c. Distribution: since Hg vapor crosses membranes more readily, a significant amount enters brain before it is oxidized.

2. Inorganic mercury salts

   a. About 10% absorbed from G.I.

   b. Concentration in RBC and plasma similar

   c. Because ionized do not readily pass blood-brain barrier or placenta

   d. High concentration in kidneys

   e. Half-life: 60 days

3. Organic mercurials

   a. About 90% absorbed from G.I.

   b. More lipid soluble - more evenly distributed and enters brain and passes placenta

   c. 5-times higher conc in RBC than plasma

   d. Half-life is 65 days

C. Acute Mercury Poisoning

   1. Local effects

D. Chronic Mercury Poisoning

   1. Central neural effects

      a. Mercury vapor (elemental mercury): largely neuro-psychiatric: depression irritability, shyness, insomnia, emotional instability, forgetfulness, confusion, excessive perspiration, uncontrolled blushing (erethism) and tremors

      b. Methylmercury

         1) Paresthesia (abnormal spontaneous sensation, ex. tingling)

2) Visual changes (constriction of visual field)

3) Hearing defects

4) Dysarthria (disturbance of articulation)

5) Ataxia

6) Fetus is extremely susceptible

d. Inorganic mercury: little known

2. Kidney: target organ of inorganic mercury toxicity

E. Diagnosis

1. Difficult: biochemical and functional aspects difficult to quantitate

2. Hg in RBC and plasma (upper normal blood 0.01 - 0.03 ug/ml, toxic symptoms at 0.2 ug/g)

3. Hg in urine (normal 25 ug/L: tremors at chlor-alkali plant at 500 ug/ml)

4. Hair: 300 X blood

III. ARSENIC (0.050 mg/L)

A. Exists in Elemental Form and in the Tri- and Pentavalent Oxidatio States

B. Toxicity Rating:

$RAs-X < As^{+5} < As^{+3} < AsH_3$
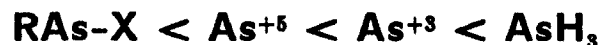
C. Absorption, Distribution and Excretion

1. Variable absorption, soluble salts well absorbed and insoluble salts are poorly absorbed

2. Distribution: liver and kidney, hair and nails

3. Methylated in body

4. Excretion

a. Excreted in urine

b. Half life about 2 days

D. Biochemical Mechanism of Toxicity

   1. As^{+3} reacts with thiols (alpha-lipoic acid)

   2. As^{+5} uncouples oxidative phosphorylation

E. Toxicological Effects

   1. Circulation: increase permeability

   2. Gastrointestinal: "rice-water" stools

   3. Kidney: glomerular capillaries

   4. Skin: "milk and roses" complexion

   5. CNS: peripheral neuritis, encephalopathy

   6. Blood: decrease in RBC and other cells

   7. Liver: fatty infiltration and necrosis

   8. Metabolic effects: not a tonic

   9. Carcinogenesis: skin and Lung (A)

F. Acute Arsenic Poisoning

   1. Early Signs and Symptoms

      a. Diarrhea

      b. Skin pigmentation

      c. Hyperkeratosis

      d. Edema of lower eyelids, face and ankles

      e. Garlic odor of breath

      F. Etc.

   2. Progression

      a. Dermatitis and keratosis of palms soles – skin cancer

      b. Enlarged liver

      c. Renal injury

      d. Peripheral neuritis (legs more than arms – contrast to lead)

        e. Encephalopathy

        f. Aplastic anemia

  H. Arsine

    1. Gas

    2. Hemolysis

IV. CADMIUM (0.005 mg/L)

  A. Occurrence and Uses

    1. Associated with lead and zinc

    2. Used as pigment

    3. Corrosion resistance – use in electroplating

    4. Cadmium-nickel batteries

    5. Coal and fossil fuels

    6. <u>Itai</u>-<u>itai</u> (ouch-ouch disease

  B. Absorption, Distribution and Excretion

    1. 1-5% absorbed from G.I.

    2. 10-40% absorbed from lung

    3. Distributes to kidney and liver – metallothionein

    4. Half-life: 10-30 yrs

    5. Excretion: bile

  C. Acute Cadmium Poisoning

    1. Oral: G.I. effects

    2. Inhalation: local irritation of respiratory tract

  D. Chronic Cadmium Poisoning

    1. Kidney

        a. Most cadmium sensitive organ

        b. Injury when 200 ùg Cd/g

      c. Quantitate by B_2-microglobulin

  2. Lungs

      a. After inhalation

      b. Emphysema (loss of ventilatory capacity and increase in lung volume)

  3. Cardiovascular: hypertension

  4. Bone

  5. Testes – sensitive after acute, not after chronic

IV. IRON

A. Frequent in children

B. G.I. tract

C. Metabolic acidosis and cardiovascular collapse

VI. OTHER METALS

A. Aluminum

  1. Low order of toxicity, aluminum hydroxide is antacid

  2. Shaver's disease – by inhalation in industry – lung fibrosis

B. Antimony: toxicity similar to arsenic

C. Barium (1.5 mg/L)

  1. Soluble salts (Cl) – G.I. and cardiovascular

  2. Insoluble salts (SO_4) – G.I. scans

  3. Convert with magnesium sulfate

D. Beryllium:

  1. Granuloma

  2. Carcinogen in animals

E. Chromium (0.12 mg/L)

1. Necessary for glucose metabolism (trivalent)

2. Insoluble hexavalent cause lung cancer by inhalation

F. Cobalt

1. Essential element in vitamin B_{12}

2. Polycythemia

3. Goiter

4. Cardiomyopathy – beer drinkers

G. Copper (1.3 mg/L)

1. Essential element

2. Wilson's disease

3. Therapy – penicillamine

H. Fluoride (4 mg/L)

1. Reduce dental caries at 0.7 – 1.2 mg/1 or ppm

2. Dental fluorosis (discoloration and/or pitting) in children above 2 ppm

3. Brittle bones at higher concentrations

4. MCD = 4 ppm
   SMCL = 2 pp.

J. Manganese

1. Managenese pneumonitis

2. CNS: Parkinson's disease

K. Nickel

1. Dermatitis (nickel itch)

2. Nickel carbonyl ($Ni[CO]_4$) – pneumonitis leukocytosis, temperature, delirium

3. Nickel subsulfide – carcinogen in man (nose)

L. Phosphorus

1. Used in matches, rat poisons, fireworks

2. G.I. upset – vomitus may be phosphorescent

3. Liver injury – jaundice

4. Chronic – necrosis of bone "phosey jaw"

M. Selenium (0.045 mg/L)

   1. Essential (glutathione peroxidase)

   2. Excess in livestock – "blind staggers or alkali disease" characterized by lack of vitality, loss of hair, sterility, atrophy of hooves, lameness and anemia

   3. Excess in main – discolored or decayed teeth, skin eruptions, G.I. distress, partial loss of hair and nails

   4. Liver injury

N. Silver

   1. Skin – argyria

O. Thallium

   1. Used in rodenticides

   2. Distributed like potassium

   3. G.I. irritation – acute

   4. Alopecia

P. Uranium

   1. Kidney injury

Q. Zinc

   1. Essential

   2. Acute oral toxicity: vomiting, diarrhea, fever

   3. Inhalation: metal fume fever – fever

PESTICIDES

I. CLASSIFICATION

    A. Insecticides

    B. Rodenticides

    C. Fungicides

    D. Herbicides

    E. Fumigants

II. INSECTICIDES

    A. Organochloride Insecticides

        1. Chlorinated ethanes

            a. DDT
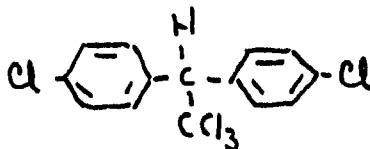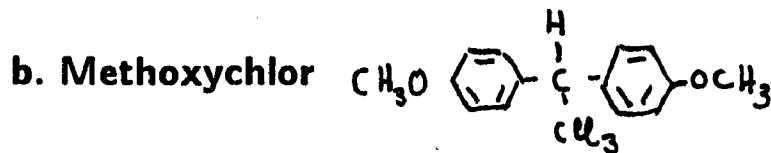

                1) high lipid solubility

                    a) stored in fat - 7 ppm

                    b) biomagnification - eggshell thinning

                    c) biotransformed - dechlorination - acid

                    d) slow elimination - 1%/day

                2) wide margin of safety

                3) Toxicology

                    a) CNS stimulation

                    b) induce P-450

                    c) hepatoma in laboratory animals

                4) Dec. 31, 1972 banned in U.S.

            b. Methoxychlor

1) Much less persistence because biotransformed by 0-demethylation

2. Chlorinated cyclodienes

    a. Examples

        1) Aldrin

        2) Dieldrin & Endrin

        3) Heptachlor

        4) Chlordane
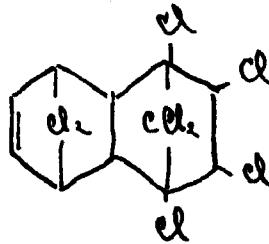
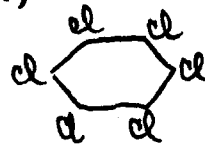   **b. Toxicology**

        1) stimulate CNS

        2) unlike DDT, have caused numerous fatalities

        3) more readily absorbed across skin

        4) lipid soluble, stored in fat, biodegraded slowly, undergo biomagnification

        5) greatest hazard of the insecticides to produce cancer

        6) registration for agricultural crops suspended in 1974 & 1976

3. Other Chlorinated Hydrocarbons

    a. Lindane (gamma isomer)

        1) Toxicology

            a) CNS stimulation

            b) induce P-450

            c) less persistent than DDT

            d) not carcinogenic

    b. Toxaphene

        1) most used insecticide in U.S.
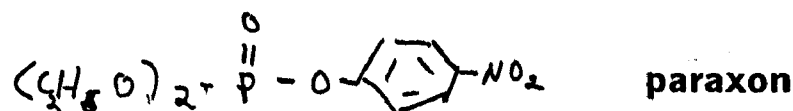
2) mixture of 175 chlorinated hydrocarbons

3) low persistence

4) recently been shown to be carcinogenic

  c. Mirex & Kepone

    1) extremely persistent

    2) like other chlorinated insecticides

       a) CNS stimulation

       b) liver injury

       c) induce P-450

       d) carcinogenic

    3) treatment – cholestyramine

B. Organophosphorus Insecticides

  1. Have largely replaced chlorinated hydrocarbon insecticides

    a. are not persistent in environment

    b. extremely low potential to produce cancer

    c. But – much higher acute toxicity in man

  2. Are derivatives of phosphoric acid – most are sulfur analogues and have to be biotransformed to an oxygen analogue to be active.

$$(C_2H_5O)_2 - \overset{\overset{S}{\|}}{P} - O -\!\!\left\langle\!\!\bigcirc\!\!\right\rangle\!\!- NO_2 \qquad \text{parathion}$$

$$(C_2H_5O)_2 - \overset{\overset{O}{\|}}{P} - O -\!\!\left\langle\!\!\bigcirc\!\!\right\rangle\!\!- NO_2 \qquad \text{paraxon}$$

  3. Inhibit cholinesterase – accumulation of acetylcholine

    a. Muscarinic – SLUD, sweating, bradycardia and hypotension

    b. Nicotinic – involuntary twitching and scattered fasciculations and eventually paralysis of the respiratory muscles.

c. CNS – confusion, ataxia, convulsions, etc.

4. Lab test – blood and plasma cholinesterase

5. Antidotes

   a. Atropine

   b. Pralidoxime (2-PAM)

6. Delayed neurotoxicity

   a. TOCP (an adulterant of Jamaica ginger)

   b. Mipafox and leptophos
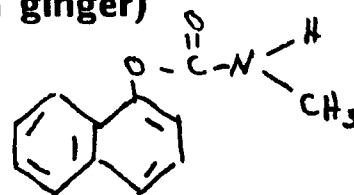
C. Carbamate Insecticides

   1. examples are carbaryl and aldicarb

   2. like organophosphates – inhibit acetylcholinesterase

   3. direct inhibitors of acetylcholinesterase

   4. carbamoylated enzyme is more readily reversible than the phosphorylated enzyme.

   5. antidotes – atropine, but not pralidoxime.

D. Botanical Insecticides

   1. Pyrethrum (Chrysanthemum)

      a. Rapid knock-down action for insects but combined with piperonyl butoxide for increased duration.

      b. Generally rated as safest insecticide

      c. Allergic properties are marked

   2. Rotenone

   3. Nicotine – most toxic insecticide – convulsions

III. FUMIGANTS – CONTROL INSECTS, RODENTS AND SOIL NEMATODES

A. Cyanide (also in silver polish, fruit seeds, laetrile)

   1. Rapid acting

2. Great affinity for iron in ferric (trivalent) state

    a. cytochrome oxidase - inhibit cellular respiration

    b. cells can't utilize oxygen

    c. respiration stimulated

    d. hypoxic convulsions

3. Therapy

    a. form ferric iron in body by forming methemoglobin - give sodium nitrite

    b. thiosulfate to give sulfur to aid rhodanese to form thiocyonate
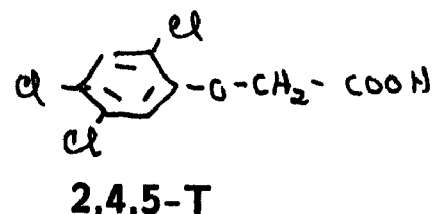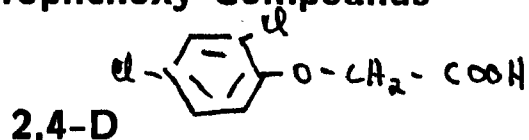
    c. oxygen

B. Methylbromide

1. Causes more deaths in California than organophosphates

2. CNS convulsions and pulmonary edema

C. Dibromochloropropane and ethylene dibromide

1. Produce CNS depression and pulmonary edema

2. Both produce malignant gastric squamous cell carcinoma

3. DBCP causes testicular injury

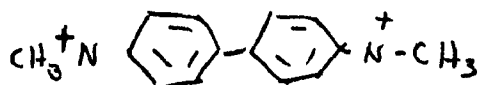# IV. HERBICIDES

A. Chlorophenoxy Compounds

2,4-D

2,4,5-T

1. Clinical reports of poisoning are rare.

2. Not cumulative chemicals - actively excreted into urine, and have T1/2 of 24 hours in man.

3. Chloracne due to TCDD
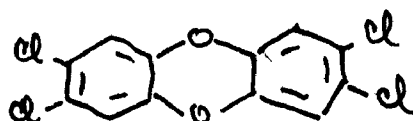
a. most toxic manufactured chemical

b. induce P-448

c. teratogen, mutagen and carcinogen

B. Dipyridyl Compounds

1. ex. paraquat

2. Lung injury

$$CH_3^+N \langle \rangle - \langle \rangle N^+ - CH_3$$

C. Triazines

1. ex: Atrazine

2. low order of toxicity

3. aminotriazole

a. antithyroid

b. thyroid cancer

D. Amides

1. ex: Alachlor (Lasso), Propachlor (Ramrod), and Propanil

2. low acute toxicity

3. have caused severe irration of the skin

4. cancer

VI. FUNGICIDES

A. Organic mercurial compounds

B. Dithiocarbamates

C. Hexachlorobenzene

1. increase P-450

2. produce porphyrea

D. Pentachlorophenol

1. uncouple oxidative phosphorylation like nitrophenol herbicides

2. fungicide in diapers has been fatal

3. commercial samples are contaminated with polychlorinated dibenzodioxins and dibenzofurans.

TOXICOLOGY OF SOLVENTS AND VAPORS

CURTIS D. KLAASSEN, PH.D.

I. GASOLINE AND KEROSENE

    A. CNS depression -- death from respiratory failure

    B. Sensitize myocardium to epinephrine -- ventricular fibrillation

    C. Aspiration -- chemical pneumonitis

II. HALOGENATED HYDROCARBONS

    A. General characteristics

        1. Excellent solvents

        2. Low flammability

        3. Depress CNS

    B. Carbon tetrachloride

        1. Use -- hookworm, anesthetic, spot remover, solvent

        2. Toxic effects

            a. CNS depression

            b. Sensitize myocardium to catecholamine

            c. Kidney injury

            d. Liver injury

                1) Mechanism

                    a) Biotransformed by P-450 to trichloromethyl free radical

                    b) Attacks membrane lipids and produces lipid peroxidation

                2) Alcohol potentiation

a) **Ethanol**

b) **Isopropanol**

e. **Carcinogenic**

C. OTHER HALOGENATED HYDROCARBONS

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

A. Methanol

   1. Used in canned fuels, some paints, paint removers, antifreeze fluids

   2. Distribution and biotransformation like ethanol

   3. Toxicology

      a. CNS depression -- but less inebriating than ethanol

      b. Acidosis -- due to oxidation to formic acid

      c. Blindness

B. Isopropanol

   1. Use -- rubbing alcohol, hand lotions, deicing and antifreeze

   2. Toxicity

      a. CNS depression -- longer lasting (biotransformed slower)

      b. Prominent gastritis

IV. GLYCOLS

A. Ethylene glycol ($OHCH_2CH_2OH$)

   1. Toxicity

      a. CNS depression

      b. Kidney injury - oxalate

V. AROMATIC HYDROCARBON SOLVENTS

A. Benzene

   1. Acute toxicity -- CNS depression

   2. Chronic toxicity
      a. Bone marrow depression -- aplastic anemia

  b. Leukemia -- humans but not in labora-
    tory animals

  c. Toxicity due to a metabolite

B. Toluene $(C_6H_5CH_3)$

 1. CNS depression

 2. Relatively safe solvent

CHEMICAL CARCINOGENS
CURTIS D. KLAASSEN, PH.D.

I. DEFINITIONS

A. Cancer: A new growth (neoplasm) -- an uncoordinated growth of cells

1. Malignant

    a. Invasive - infiltration into surrounding tissue

    b. Metastatic - gives rise to secondary discontinuous tumor growth

    c. Growth - rapid

2. Benign

    a. Noninvasive and therefore compresses surrounding tissue forming capsule

    b. Nonmetastic, remains local

    c. Slow and relatively limited growth

    d. Close resemblance to cell of origin

II. HISTORICAL

A. Chimney sweeps had cancer of scrotum -- late 18th century

B. Dye workers -- aromatic animes -- cancer of urinary bladder

III. TWO-STAGE CARCINOGENESIS (CO-CARCINOGENESIS)

A. Initiation: production of an irreversible cellular damage

B. Promotion: process whereby a tumor is caused to develop in which initiation has already occurred.

C. Complete carcinogen: does both initiation and promotion

IV. CLASSES OF CARCINOGENIC CHEMICALS

A. Genotoxic – binds to DNA

   1. Direct acting or primary carcinogen

   2. Procarcinogen or secondary carcinogen

   3. Inorganic carcinogen

B. Epigenetic

   1. Solid state carcinogen

   2. Hormones

   3. Immunosuppressor

   4. Co-carcinogen

   5. Promoter

V. DIRECT-ACTING, OR PRIMARY CARCINOGENS

A. Highly chemical reactive

B. Examples

   1. Bis(Chloromethyl)ether -- $ClCH_2OCH_2Cl$

   2. Methyl iodide

   3. Dimethyl sulfate

VI. PROCARCINOGENS OR SECONDARY CARCINOGENS

A. The ultimate carcinogen results from metabolic activation (the final active forms are electron-deficient or Electrophiles – these electrophiles combine with electron-rich or Nucleophiles in nucleic acids to form covalent bonds)

Little is known of how this interaction ultimately transforms the cell into a cancer cell. It may alter gene expression and activate oncogenes.

B. Examples

   1. Polycyclic or heterocyclic aromatic hydrocarbons

      a. Benzo(a)pyrene, 3-methylcholanthrene, 7,12-dimethylbenz(a)anthracene

b. Natural products in incomplete combustion such as in soot, coal, tar, tobacco smoke, petroleum and charcoal

2. Aromatic amines

   a. Aniline cancers in dyestuff manufacture

   b. 2-acetylaminofluorene (AAF)

   c. 2-naphthylamine

   d. 4-biphenylamine

   e. 3-aminotriazole

   f. Benzidine

   g. Pyrolysis of protein-containing material

3. Azo dyes

   a. 4-dimethylaminoazobenzene (butter yellow)

   b. Amaranth -- red dye #2

4. Nitrosamine and nitrosamides

   a. Nitrosamine

   b. Dimethylnitrosamine

   c. Streptozotocin

5. Dioxane

6. Benzene - leukemia

7. Urethane

8. Carbon tetrachloride, chloroform, DDT, Tris(2,3-dibromopropyl)-phosphate, vinyl chloride ($CH_2=CHCl$)

9. Microbiologic carcinogens

   a. Mycotoxins

      Aflatoxin B_1 (B_2, G_1, G_2)

10. Plant carcinogens

      a. Tobacco – some carcinogens, some pyrolysis products, promoter

      b. Safrole

      c. Senecio (se-ne-she o) (pyrolizidine) alkaloids

VII. INORGANIC CARCINOGENS

A. Uranium

B. Polonium

C. Radium

D. Nickel

E. Titanium

F. Arsenic

VIII. SOLID STATE CARCINOGENS

A. Size and shape

B. Asbestos -- mesotheliomas

IX. HORMONES

A. Estrogens

    1. Estradiol – not genotoxic – promoter

    2. Diethylstilbestrol

X. IMMUNOSUPPRESSIVE DRUGS

XI. CO-CARCINOGENS: AGENTS THAT INCREASE THE OVERALL CARCINOGENIC PROCESS CAUSED BY A GENOTOXIC CARCINOGEN WHEN ADMINISTERED WITH THE CARCINOGEN

A. Mechanisms of co-carcinogenesis

    1. Altering biotransformation

    2. Increasing cell growth

    3. Increasing uptake of carcinogen

4. Depletion of competing nucleophiles

5. Inhibit DNA repair

B. Examples

    1. Croton oil (phorbol esters)

    2. Tobacacco smoke (catechol)

XII. PROMOTERS; AGENTS THAT INCREASE THE TUMORIGENIC RESPONSE TO A GENOTOXIC CARCINOGEN WHEN APPLIED AFTER THE CARCINOGEN

A. Examples

    1. Croton oil – phorbol esters, TPA (12-0-tetradecanoylphorbol-13-acetate)

   2. Bile acids

    3. Phenobarbital, DDT, BHT

B. How to test for promoters

    1. Two-state skin tumorigenesis: give carcinogen (ex: 7,12-dimethylbenz(a)anthracene then repeated administration of promoting agent (often twice a week) over 2-5 months

    2. Pitot and Farber liver methods: Do 2/3 hepatectomy, give genotixc chemical and then promoter and look for increase in number of preneoplastic nodules

XIII. PHARMACOLOGICAL AND TOXICOLOGICAL IMPLICATIONS

A. Dose response
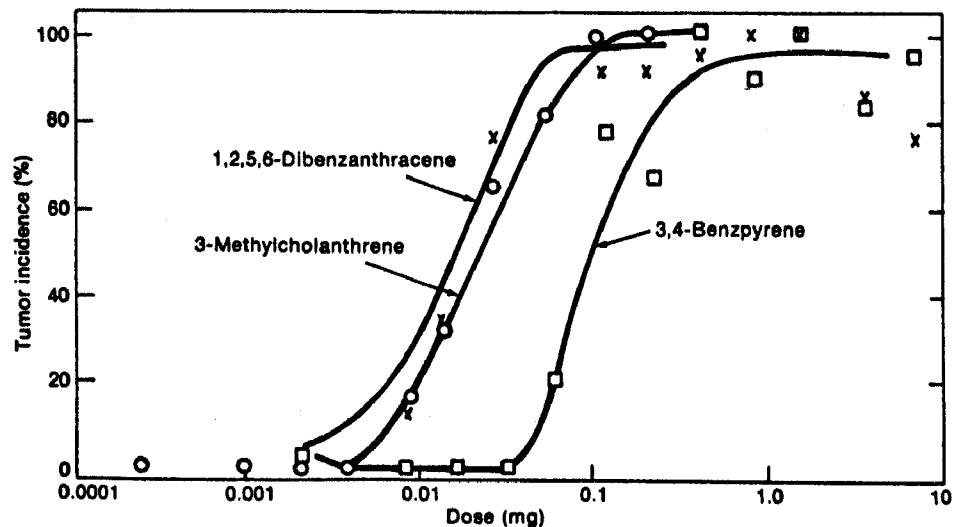
B. Species and strain

    1. Species – benzidene in man affects bladder: in rat the liver

    2. Age – younger more susceptible, DES transplacenta

XIV. DETECTION OF CHEMICAL CARCINOGENS

A. Structure of chemical

B. In _vitro_ short term tests (genotoxic)

    1. Bacterial mutagenesis (ex, Ames)

    2. DNA repair

    3. Mammalian mutagenesis

    4. Sister chromatid exchange

    5. Cell transformation

C. Limited _in vivo_ bioassays

    1. Skin tumor induction in mice

    2. Pulmonary tumor induction in mice (30–35 weeks)

    3. Breast cancer induction in female Sprague-Dawley rats

    4. Altered foci induction in rodent liver

        (Gamma-glutamyl transpeptidase, glucose-6-phosphatase, adenosine triphosphatase, resistance to iron accumulation, P-450, glucuronosyltransferase) -- 12 weeks, last 2 weeks plus iron

D. Chronic bioassay

XV. EPA PROPOSED CLASSIFICATION OF CARCINOGENS

A. Human carcinogen

B. Probable human carcinogen

    B1. Limited human data, sufficient animal data

B2. Sufficient animal data

C. **Possible human carcinogen – limited animal data**

D. **Not classified – inadequate or no data**

E. **No evidence for carcinogenicity in humans – data in animals indicates the chemical is not carcinogenic**

I. PRINCIPLES OF RISK ASSESSMENT

A Nontechnical Review

WORKSHOP ON RISK ASSESSMENT

United States Environmental Protection Agency

I.

Principles of Risk Assessment: A Nontechnical Review

CONTENTS

I. INTRODUCTION

This report provides general background information for understanding the types of scientific data and methods currently used to assess the human health risks of environmental chemicals. Human health risk is the likelihood (or probability) that a given chemical exposure or series of exposures may damage the health of exposed individuals. Chemical risk assessment involves the analysis of exposures that have taken place in the past, the adverse health effects of which may or may not have already occurred. It also involves prediction of the likely consequences of exposures that have not yet occurred. This document is by no means a complete survey of the complex subject of risk assessment, but it is sufficiently comprehensive to assist conference participants in dealing with the specific sets of data relevant to the case study.

The report begins with a discussion of the four major components of risk assessment and their interrelationships. This section is followed by extensive discussion of these four major components. Generally, each section focuses on the methods and tests used to gather data, the principles used for data interpretation, and the uncertainties in both the data and inferences drawn from them. Throughout these discussions, key concepts (e.g., exposure, dose, thresholds, and extrapolation) are defined and extended descriptions provided.

Many of the principles discussed in this report are widely accepted in the scientific community. Others (e.g., thresholds for carcinogens, the utility of negative epidemiology data) are controversial. In such cases we have attempted to describe the various points of view and the reasons for them and have also identified the viewpoint that seems to have been broadly adopted by public health and regulatory officials.

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

II. RISK AND RISK ASSESSMENT

BASIC CONCEPTS AND DEFINITIONS

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

All human activities carry some degree of risk. Many risks are known with a relatively high degree of accuracy, because we have collected data on their historical occurrence. Table 1 lists the risks of some common activities.

Table 1

ANNUAL RISK OF DEATH FROM SELECTED COMMON HUMAN ACTIVITIES[1]

	Number of Deaths in Representative Year	Individual Risk/Year		Lifetime Risk[2]
Coal Mining				
Accident	180	1.30×10^{-3}	or 1/770	1/17
Black lung disease	1,135	8×10^{-3}	or 1/125	1/3
Motor Vehicle	46,000	2.2×10^{-4}	or 1/4,500	1/65
Truck Driving	400	10^{-4}	or 1/10,000	1/222
Falls	16,339	7.7×10^{-5}	or 1/13,000	1/186
Home Accidents	25,000	1.2×10^{-5}	or 1/83,000	1/130

[1]Selected from Hutt (1978) Food, Drug, Cosmetic Law J. 33:558-589.
[2]Estimated based upon 70-year lifetime and 45-year work exposure.

The risks associated with many other activities, including the exposure to various chemical substances, can not be readily assessed and quantified. Although there are considerable historical data on the risks of some types of chemical exposures (e.g., the annual risk of death from intentional overdoses or accidental exposures to drugs, pesticides, and industrial chemicals), such data are generally restricted to those situations in which a single, very high exposure resulted in an immediately observable form of injury, thus leaving little doubt about causation. Assessment of the risks of levels of chemical exposure that do

not cause immediately observable forms of injury or disease (or only minor forms such as transient eye or skin irritation) is far more complex, irrespective of whether the exposure may have been brief, extended but intermittent, or extended and continuous. It is the latter type of risk assessment activity that is reviewed in this report (although some review of acute poisoning is also included).

As recently defined by the National Academy of Sciences, risk assessment is the scientific activity of evaluating the toxic properties of a chemical and the conditions of human exposure to it in order both to ascertain the likelihood that exposed humans will be adversely affected, and to characterize the nature of the effects they may experience.[1]

The Academy distinguishes risk assessment from risk management; the latter activity concerns decisions about whether an assessed risk is sufficiently high to present a public health concern and about the appropriate means for control of a risk judged to be significant.

The term "safe," in its common usage, means "without risk." In technical terms, however, this common usage is misleading because science can not ascertain the conditions under which a given chemical exposure is likely to be absolutely without a risk of any type. The latter condition--zero risk--is simply immeasurable. Science can, however, describe the conditions under which risks are so low that they would generally be considered to be of no practical consequence to persons in a population. As a technical matter, the safety of chemical substances--whether in food, drinking water, air, or the workplace--has always been defined as a condition of exposure under which there is a "practical certainty" that no harm will result in exposed individuals. (As described later, these conditions usually incorporate large safety factors, so that even more intense exposures than those defined as safe may also carry extremely low risks). We note that most "safe" exposure levels established in the way we have described are probably risk-free, but science simply has no tools to prove the existence of what is essentially a negative condition.

Another preliminary concept concerns classification of chemical substances as either "safe" or unsafe" (or as "toxic" and "nontoxic"). This type of classification, while common (even among scientists who should know better), is highly problematic

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[1]Risk Assessment in the Federal Government: Managing the Process (Washington, D.C.: National Academy Press, 1983).

and misleading. All substances, even those which we consume in high amounts every day, can be made to produce a toxic response under some conditions of exposure. In this sense, all substances are toxic. The important question is not simply that of toxicity, but rather that of risk--i.e., what is the probability that the toxic properties of a chemical will be realized under actual or anticipated conditions of human exposure? To answer the latter question requires far more extensive data and evaluation than the characterization of toxicity.[2]

THE COMPONENTS OF RISK ASSESSMENT

There are four components to every (complete) risk assessment:

A. **Hazard Identification**--Involves gathering and evaluating data on the types of health injury or disease that may be produced by a chemical and on the conditions of exposure under which injury or disease is produced. It may also involve characterization of the behavior of a chemical within the body and the interactions it undergoes with organs, cells, or even parts of cells. Data of the latter types 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; we are simply determining whether it is scientifically correct to infer that toxic effects observed in one setting will occur in other settings (e.g., are substances found to be carcinogenic or teratogenic in experimental animals likely to have the same result in humans?).

B. **Dose-Response Evaluation**--Involves describing the quantitative relationship between the amount of exposure to a substance and the extent of toxic injury or disease. Data derive from animal studies or, less frequently, from studies in exposed human populations. There may be many different dose-response relationships for a substance if it produces different toxic effects under

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

different conditions of exposure. The risks of a substance can not be ascertained with any degree of confidence unless dose-response relations are quantified, even if the substance is known to be "toxic."

C. __Human Exposure Evaluation__--Involves describing the nature and size of the population exposed to a substance and the magnitude and duration of their exposure. The evaluation could concern past or current exposures, or exposures anticipated in the future.

D. __Risk Characterization__--Generally involves the integration of the data and analysis of the first three components to determine the likelihood that humans will experience any of the various forms of toxicity associated with a substance. (In cases where exposure data are not available, hypothetical risk can be characterized by the integration of hazard identification and does-response evaluation data alone.)

The next four sections elaborate on each of these components of risk assessment. However, the concept of "dose," which underlies all the discussions to follow of both experimental animals and human populations, is reviewed first.

DOSE

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

In both human and animal exposures, two types of measurement must be distinguished:

1. Measurement of the amount of the substance in the medium (air, diet, etc.) in which it is present or administered.

2. Measurement of the amount received by the subject, whether human or animal.

It is critically important to distinguish these two types of measures. The second measure, which is usually expressed as a dose, is the critical factor in assessing risk. The first measure, along with other information, usually is essential if the dose is to be established. It may be substituted or supplemented, however, in cases where environmental modeling or biomonitoring data are available.

The difference between these two measures is best described by example. Suppose a substance is present in drinking water to be consumed by an individual. To determine the individual's dose of this substance, it is first necessary to know the amount present in a given volume of water. For many environmental substances, the amounts present fall in the milligram (mg, one-thousandth of a gram = 1/28571 ounce) or microgram (μg, one-millionth of a gram = 1/28,571,429 ounce) range. The analyst will usually report the number of mg or μg of the substance present in one liter of water, i.e., mg/l or μg/l. These two units are sometimes expressed as parts per million (ppm) or parts per billion (ppb), respectively.[3]

Given the concentration of a substance in water (say in ppm), it is possible to estimate the amount an individual will consume by knowing the amount of water he drinks. Time is another important factor in determining risk, so the amount of water consumed per unit time is of interest. In most public health evaluations, it is assumed that an individual consumes 2 liters of water each day through all uses. Thus, if a substance is present at 10 ppm in water, the average daily individual intake of the substance is obtained as follows:

10 mg/liter x 2 liter/day = 20 mg/day

For toxicity comparisons among different species, it is necessary to take into account size differences, usually by dividing daily intake by the weight of the individual. Thus, for a man of average weight (usually assumed to be 70 kilograms (kg) or 154 pounds), the daily dose of our hypothetical substance is:

20 mg/day ÷ 70 kg = 0.29 mg/kg/day

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

For a person of lower weight (e.g., a female or child), the daily dose at the same intake rate would be larger. For example, a 50 kg woman ingesting the hypothetical substance would receive a dose of:

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

A child of 10 kg could receive a dose of 2.0 mg/kg/day, although it must be remembered that such a child would drink less water each day (say, 1 liter), so that the child's dose would be:

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

Also, laboratory animals, usually rats or mice, receive a much higher dose than humans at the same daily intake rate because of their much smaller body weights (of course, rats and mice do not drink 2 liters of water each day!).

These sample calculations point out the difference between measurement of environmental concentrations and dose, at least for drinking water. The relationships between measured environmental concentrations and dose are more complex for air and other media. Table 2 lists the data necessary to obtain dose from data on the concentration of a substance in water. Each medium of exposure must be treated separately and some calculations are more complex than in the dose per liter of water example.

Table 2

DATA AND ASSUMPTIONS NECESSARY TO ESTIMATE
HUMAN DOSE OF A WATER CONTAMINANT FROM KNOWLEDGE OF ITS CONCENTRATION

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

1. Direct Ingestion Through Drinking

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

2. 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.

3. Skin Absorption from Water

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

4. Ingestion of Contaminated Food

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

5. Skin Absorption for Contaminated Soil

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

It is important always to consider that a human may be simultaneously exposed to the same substance through several media. That is, a dose may be received through more than one route of exposure (inhalation, ingestion, dermal contact). The "total dose" received by an individual is the sum of doses received by each individual route (see the example in Table 2).

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

Two additional factors concerning dose require special attention. The first is the concept of absorption (or absorbed dose). The second concerns inferences to be drawn from toxicities observed under one route of exposure for purposes of predicting the likelihood of toxicity under other routes.
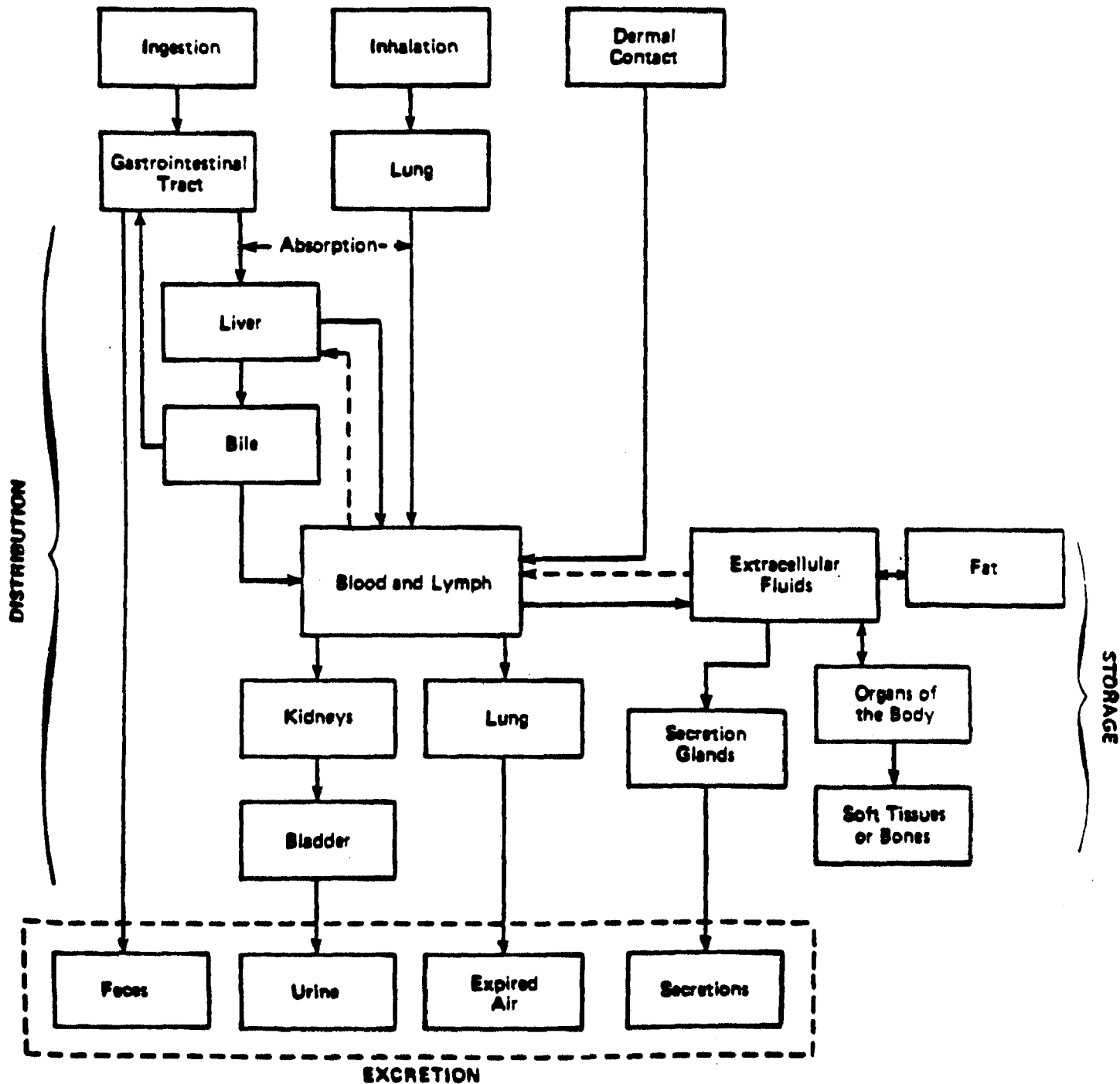
Absorption

When a substance is ingested in the diet or in drinking water, it enters the gastrointestinal tract. When it is present in air (as a gas, aerosol, particle, dust, fume, etc.) it enters the upper airways and lungs. A substance may also come into contact with the skin and other body surfaces as a liquid or solid. Some substances may cause toxic injury at the point of initial contact (skin, gastrointestinal tract, upper airways, lungs, eyes). Indeed, at high concentrations, most substances will cause at least irritation at these points of contact. But for many substances, toxicity occurs after they pass through certain barriers (e.g., the wall of the gastrointestinal tract or the skin itself), enter blood or lymph, and gain access to the various organs or systems of the body. Figure 1 is a diagram of some of the important routes of absorption. This figure also shows that chemicals may be distributed in the body in various ways and then excreted. (However, some chemical types—usually substances with high solubility in fat, such as DDT—are stored for long periods of time, usually in fat.)

Figure 1

KEY ROUTES OF CHEMICAL ABSORPTION, DISTRIBUTION, AND EXCRETION

Some chemicals undergo chemical change (metabolism) within the cells of the body before excretion.
Toxicity may be produced by the chemical as introduced, or by one or more metabolites.

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

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

Interspecies Differences in Exposure Route

As described later, a critical feature of risk characterization is a comparison of doses that are toxic in experimental animals and the doses received by exposed humans. If humans are exposed by the same route as the experimental animals, it is frequently assumed (in the absence of data) that the extent of absorption in animals and humans is approximately the same; under such an assumption, it is unnecessary to estimate the absorbed dose by taking absorption rate into account. However, humans are often exposed by a different route than that used to obtain toxicity data in experimental animals. If the observed toxic effect is a systemic one, it may be appropriate to infer the possibility of human toxicity even under the different exposure route. Before doing so, however, it is critical to consider the relative degrees of absorption by different exposure routes. For example, if a substance is administered orally to a test animal but human exposure is usually by inhalation, knowledge of the percentage absorbed orally by the animal and by inhalation in humans is necessary to properly compare human and animal doses. These calculations and underlying assumptions are too complex for discussion here, but they should be kept in mind when risks are being described.

In the following discussion of the components of risk assessment, we shall use the term dose only as described. Many risk assessors use the terms exposure and dose synonomously. In this document, however, the term exposure describes contact with a

substance (e.g., we say that animals are _exposed_ to air contain-
ing 10 mg/m^3, of a compound), as well as the size of the dose,
the duration of exposure, and the nature and size of the exposed
population. In our usage, exposure is a broader term than dose.
Although our usages of those terms are technically correct, it
should be recognized that some assessors use the term exposure to
mean dose (although the reverse is not true).

III. HAZARD IDENTIFICATION

INTRODUCTION

Information on the toxic properties of chemical substances is obtained from 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 (e.g., 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 (e.g., the earliest signs that benzene was a human leukemogen 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 epidemiology studies. These two types of investigation are not only principal sources of data, but also present interpretative difficulties, some rather subtle, some highly controversial.

TOXICITY INFORMATION FROM ANIMAL STUDIES

The Use of Animal Toxicity Data

Animal toxicity studies are conducted based primarily on the longstanding assumption that effects in humans can be inferred from effects in animals. In fact, this assumption has been shown to be generally correct. Thus, all 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. In addition, the acutely toxic doses of many chemicals are similar in humans and a variety of experimental animals. This principle of extrapolation of animal data to humans has been widely accepted in the scientific and regulatory communities. The foundation of our ability to infer effects in humans from effects in animals has been attributed to the evolutionary relationships and the phylogenetic continuity of animal species including man. Thus, at least among mammals, the basic anatomical, physiological, and biochemical parameters are similar across species.

However, although the general principle of inferring effects in humans from effects in experimental animals is well founded, there have been a number of exceptions. Many of these exceptions relate to differences in the way various species handle a chemical to which they are exposed 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 in inferring human toxicity from animal toxicologic study results.

In the particular case of evaluation of long-term animal studies conducted primarily to assess the carcinogenic potential of a compound, certain general observations increase the overall strength of the evidence that the compound is carcinogenic. With an increase in the number of tissue sites affected by the agent, there is an increase in the strength of the evidence. Similarly, an increase in the number of animal species, strains, and sexes showing a carcinogenic response will increase the strength of the evidence of carcinogenicity. Other aspects of importance are the occurrence of clear-cut dose-response relationships in the data evaluated; the achievement of a high level of statistical signif-icance of the increase of tumor incidence in treated versus control animals; dose-related shortening of the time-to-tumor occurrence or time-to-death with tumor; and a dose-related increase in the proportion of tumors that are malignant. The following sections describe the general nature of animal toxicity studies, including major areas of importance in their design, conduct, and interpretation. Particular consideration will be given to the uncertainties involved in the evaluation of their results.

General Nature of Animal Toxicity Studies

Toxicity studies are conducted to identify the nature of health damage produced by a substance[4] 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 necessary to calculate doses that will not be lethal to animals used in toxicity studies of longer durations. Moreover, such

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[4]We use the term substance to refer 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 tested substance before drawing inferences about the toxicity of other samples of the same substance that might have a somewhat different composition.

studies will give one 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, on average, for 50% of an exposed population). In a group of chemicals, those exhibiting lower $LD_{50}s$ are more acutely toxic than those with higher values. A group of well-known substances and their LD_{50} values are listed in Table 3.

Table 3

APPROXIMATE ORAL $LD_{50}s$ IN RATS FOR A
GROUP OF WELL-KNOWN CHEMICALS[1,2]

Chemical	LD_{50}(mg/kg)
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

[1] Selected from NIOSH, Registry of Toxic Effects of Chemical Substances, 1979. Results reported elsewhere may differ.
[2] Compounds are listed in order of increasing toxicity—i.e., sucrose is the least toxic and strychnine is the most toxic.

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 dosed in the same way will get sick but will recover, and still others will not appear to be affected at all. We shall return to this point after a fuller discussion of other forms of toxicity.

Each of the many different types of toxicology studies has a different purpose. Animals may be exposed repeatedly or continuously for several weeks or months (subchronic toxicity studies) or for close to their full lifetimes (chronic toxicity studies) to learn how the period of exposure affects toxic response. In general, the reasons to conduct toxicity studies can be summarized as follows:

- Identify the specific organs or systems of the body that may be damaged by a substance.

- Identify specific abnormalities or diseases that a substance may produce, such as cancer, birth defects, nervous disorders, or behavioral problems.

- Establish the conditions of exposure and dose that give rise to specific forms of damage or disease.

- Identify the specific nature and course of the injury or disease produced by a substance.

- Identify the biological processes that underlie the production of observable damage or disease.

The laboratory methods needed to accomplish many of these goals have been in use for many years, although some methods are still being developed. Before describing some of the tests, it is useful to say more about the various manifestations of toxicity.

Manifestations of Toxicity

Toxic responses, regardless of the organ or system in which they occur, can be of several types. For some, the severity of the injury increases as the dose increases. Thus, for example, some chemicals affect the liver. At high doses they may kill liver cells, perhaps so many as to destroy the liver and thus cause the deaths of some or all experimental subjects. As the dose is lowered, fewer cells may be killed, but they may exhibit other forms of damage, causing imperfections in their functioning. At lower doses still, no cell deaths may occur and there

may be only slight alterations in cell function or structure. 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," there is no clear consensus on this issue.) One of the goals of toxicity studies is to determine the "no observed effect level" (NOEL), which is the dose at which no effect is seen; the role of the NOEL in risk assessment is discussed later.

In other cases, the severity of an effect may not increase with dose, but the _incidence_ of the effect will increase with increasing dose. In such cases, the number of animals experiencing an adverse effect at a given dose is less than the total number, and, as the dose increases, the fraction experiencing adverse effects (i.e., the incidence of disease or injury) increases; at sufficiently high dose, all experimental subjects will experience the effect. The latter responses are properly characterized as probabilistic. Increasing the dose increases the probability (i.e., risk) that the abnormality will develop in an exposed population. Often with toxic effects, including cancer, both the severity and the incidence increase as the level of exposure is raised. 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.

Generally, as the duration of exposure increases, both the NOEL and the doses at which effects appear decrease; in some cases, new effects not apparent upon exposures of short duration become manifest.

Toxic responses also vary in degree of reversibility. In some cases, an effect will disappear almost immediately following cessation of exposure. At the other extreme, some exposures will result in a permanent injury--for example, a severe birth defect resulting from a substance that irreversibly damages a fetus at a critical moment of its development. Most toxic responses fall somewhere between these extremes. In many experiments, however, the degree of reversibility cannot be ascertained by the investigator.

Seriousness is another characteristic of a toxic response. 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, it will not be at all clear 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 that has not been fully clarified.

Design and Conduct of Toxicity Tests

Toxicity experiments vary widely in design and conduct. Although there are relatively well standardized tests for various types of toxicity (e.g., National Cancer Institute carcinogenicity bioassays) developed by regulatory and public agencies in connection with the premarket testing requirements imposed on certain classes of chemicals, large numbers of other tests and research-oriented investigations are conducted using specialized study designs (e.g., carcinogenicity assays in fish). In this section, we present a few of the critical considerations that enter into the design of toxicity experiments. However, there are numerous variations on the general themes we describe.

Selection of Animal Species

Rodents, usually rats or mice, are the most commonly used laboratory animals for toxicity testing. Other rodents (e.g., hamsters and guinea pigs) are sometimes used, and many experiments are conducted using rabbits, dogs, and such nonhuman primates as monkeys or baboons. For example, although nonhuman primates may be chosen for some reproductive studies 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.

Rats and mice are the most common choice because they are inexpensive and can be handled relatively easily. Furthermore, such factors as genetic background and disease susceptibility are well established for these species. The full lifespans of these smaller rodents are complete in two to three years, so that the effects of lifetime exposure to a substance can be measured relatively quickly (as compared to the much longer-lived dog or monkey).

Dose and Duration

An LD_{50} using high doses of the substance is frequently the first toxicity experiment performed. After completing these experiments, investigators study the effects of lower doses

administered over longer periods. The purpose is to find the range of doses over which adverse effects occur and to identify the NOEL for these effects (although the latter 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 all doses administered, the toxic properties of the substances will not have been characterized, and the investigator will usually repeat the experiment at higher doses or will extend its duration.[5]

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

Number of Dose Levels

Although it is desirable that many different dose levels be used 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 leave great uncertainty about the full range of doses over which effects are expected.

Controls

No toxicity experiment is interpretable if control animals are omitted. Control animals must be of the same species, strain, sex, age, and state of health as the treated animals, and must be held under identical conditions throughout the experiment. (Indeed, allocation of animals to control and treatment groups should be performed on a completely random basis.) Of course, the control animals are not exposed to the substance under test.

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[5]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. As a practical matter, the highest level of a compound fed to an animal in toxicity studies is 5% of the diet, even if no toxic effect is seen at this level.

Route of Exposure

Animals are usually exposed by a route that is as close as possible to that through which humans will be exposed, because the purpose of most such tests is to produce the data upon which human safety decisions will be based. 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 chemicals 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.

Specialized Designs

Generally, the toxicologist exposes test animals and simply records whatever effects happen to occur under the conditions of the experiment. If, however, it is decided that certain highly specific hypotheses about a substance are to be tested (e.g., does the substance cause birth defects or does it affect the immune system?), certain specialized designs must be used. Thus, for example, the hypothesis that a chemical is teratogenic (causes birth defects) can be tested only if pregnant females are exposed at certain critical times during pregnancy.

One of the most complex of the specialized tests is the carcinogenesis bioassay. These experiments are used to test the hypothesis of carcinogenicity--that is, the capacity of a substance to produce tumors. Because of the importance of the carcinogenesis bioassay, a full section is devoted to it. We shall then discuss, in turn, controversial issues in the design of animal tests and interpretation of test results.

Design of Tests for Carcinogenicity

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 carcinogenicity testing, but one critical design issue that has been highly controversial requires extensive discussion. The issue is the concept of maximum tolerated dose (MTD), which is defined as the maximum dose that an animal species can tolerate for a major portion of its lifetime without significant impairment of growth or observable toxic effect other than carcinogenicity. Cancer can take most of a lifetime to develop, and it is thus widely agreed that studies should be designed so that the animals survive in relatively good health for a normal lifetime. It is not so widely agreed, however, that

the MTD, as currently used, is the best way to achieve this objective. The MTD and half the MTD are the usual doses used in the NCI carcinogenicity bioassay.

The main reason cited for using the MTD as the highest dose in the bioassay is that experimental studies are conducted on a small scale, making them "statistically insensitive," and that very high doses overcome this problem. For practical reasons, experimental studies 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 incidence of cancer as a function of dose (including control animal incidence) is tabulated by the examining pathologists. 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 treatment with the substance.

In an experiment of about 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%, or 3 animals with tumors in a test group of 60 animals. If control animals develop tumors (as they frequently do), the lowest range of cancer incidence detectability is even higher. A cancer incidence of 5% is very high, yet ordinary experimental studies are not capable of detecting lower rates and most are even less sensitive.

MTD advocates 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 by the study. MTD critics do not reject the notion that animal experiments may be statistically insensitive, but rather are concerned about the biological implications of such high doses.

Concerns about use of MTDs can be summarized: (1) the underlying biological mechanisms that lead to the production of cancer may change as the dose of the carcinogen changes; (2) current methods for estimating an MTD for use in an experiment do not usually take these mechanisms into account; (3) the biological mechanisms at work under conditions of actual human exposure may be quite different from those at work at or near the MTD; and (4) therefore, observations at or near an MTD (as determined by current methods) may not be qualitatively relevant to conditions of actual human exposure.

Many 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 they are frequently disregarded in designing studies and interpreting data. Although there are occasional attempts to develop a more biologically relevant definition of MTD, most current tests (e.g., those carried out by the National Toxicology Program) use a definition of MTD that does not take biological mechanisms into account.

This state of affairs is not likely to change. Those who promote the use of MTD, as currently defined, frequently argue that if the highest dose used was not the MTD, failure to observe a carcinogenic effect in a given experiment does not permit the conclusion that the tested substance is not carcinogenic. A similar argument is made if the survival of the test animals did not approximate their full lifetimes.

Conduct and Interpretation of Toxicity Tests

Many factors must be considered in the conduct of toxicity tests to ensure their success and the utility of their results. In evaluating the results of such tests, certain questions must be asked about the design and conduct of a test to ensure critical appraisal. The major questions include the following:

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 (e.g., 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?

12. Were the statistical tests used appropriate 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 and other types of questions were examined and would include a list of qualifications on test results in areas where answers were missing or unsatisfactory.

Categorization of Toxic Effects

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

The toxic characteristics of a substance are usually categorized according to the organs or systems they affect (e.g., liver, kidney, nervous system) or the diseases they cause (e.g., cancer, birth defects). The most commonly used categorizations of toxicity are briefly described in Appendix I.

Although there are uncertainties associated with most evaluations of animal toxicity data, there are some special problems associated with interpretation of carcinogenicity data. Because these problems are the source of much controversy, we afford them special attention in the next section.

Uncertainties in Evaluation
of Animal Carcinogenicity
Test Results

One area of uncertainty and controversy concerns the occurrence of certain types of tumors in control animals. In most animal experiments, control animals will also develop tumors, and interpretation of such experiments depends on comparing the incidence of tumors in control animals with that observed in treated animals. In some instances, this is not as straightforward as it may seem. 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% to a high of about 40%; the average rate is about 14%. Suppose that, in a particular experiment, male mice treated with a substance exhibited a 35% incidence of lung tumors, and control animals exhibited an incidence of 8%. Statistical analysis of such data would show that the treated animals experienced a statistically significant increase in tumor incidence, and the substance producing this effect might be labeled a lung carcinogen.

Further analysis of the incidence data suggests that such a statistical analysis may be misleading. The 35% incidence observed in treated animals is within the range of tumor incidence that is normally experienced by male mice, although the particular group of male mice used as controls in this experiment exhibited an incidence in the low end of the normal range. Under such circumstances, use of the simple statistical test of significance might be misleading and result in the erroneous labeling of a substance as a carcinogen.

Another major area of uncertainty arises 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. There is usually no significant controversy about 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 it is not always clear they should be considered indicators of a carcinogenic process. Some tumors will remain benign for the lifetime of the animal, but in some cases they have been observed to progress to malignancy. Generally, the numbers of animals with benign tumors that are thought to be part of the carcinogenic process are combined with those having malignancies to establish the total tumor incidence. Many pathologists disagree with such combining, and there appears to be no end to the controversy in this area. The issue has been especially controversial in connection with tumors found in rodent livers.

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, other experimental techniques have become available and, although none is yet considered definitive, they may provide important information.

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_ (outside the animal--e.g., bacterial cells as in the Ames mutagenicity assay) and _in vivo_ (within the animal) assays for chromosomal mutations in animals' cells. In addition to these rapid (test-tube) tests, several tests of intermediate duration involving whole animals have been used. These include the induction of skin and lung tumors in mice, breast cancer in female certain species of 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 increasingly important roles 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 underlying the production of tumors. They have not been definitively correlated with results in animal models, however, and regulatory agencies and other public health institutions do not consider positive or negative results in these systems as definitive indicators of carcinogenicity or the lack thereof, but only as ancillary evidence.

DATA FROM HUMAN STUDIES

Information on adverse health effects in human populations is obtained from four sources: (1) summaries of self-reported symptoms in exposed persons; (2) case reports prepared by medical personnel; (3) correlational 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 study can be characterized as descriptive epidemiology and are often useful in drawing attention to previously unsuspected problems. Although they cannot identify a cause-and-effect relationship, they have value in generating hypotheses that can be further tested. Epidemiologic studies involve comparing the health status of a group of persons who have been exposed to a suspected agent with that of a comparable nonexposed group.

Most epidemiology studies are either case-control studies or cohort studies. In case-control studies, a group of individuals with a specific disease is identified and an attempt is made to ascertain commonalities in exposures they may have experienced in the past. The carcinogenic properties of DES were discovered through such studies. In cohort studies, the health status of individuals known to have had a common exposure is examined 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 these types. Generally, epidemiologists have turned to occupational settings or to patients treated with certain drugs to conduct their studies.

When epidemiological investigations yield convincing results, they are enormously beneficial because they 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 in the evaluation of the total database. Although no study can provide complete assurance that no risk exists, negative data from epidemiological studies of sufficient size can be used to establish the level of risk that exposure to an agent almost assuredly will not exceed.

Although epidemiology studies are powerful when clearcut differences exist, several points must be considered when their results are interpreted:

- Appropriately matched control groups are difficult to identify, because the factors that lead to the exposure of the study group (e.g., occupation or residence) are often associated with other factors that affect health status (e.g., lifestyle and socioeconomic status).

- It is difficult to control for related risk factors (e.g., cigarette smoking) that have strong effects on health.

- 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 illnesses 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 relations is thus frequently impossible.

- For investigation of diseases that take many years to develop, such as cancer, it is necessary to 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 is limited, unless very large populations are studied.

For these reasons, epidemiological studies are subject to sometimes extreme uncertainties. It is usually necessary to have independent confirmatory evidence, such as a concordant result in a second epidemiological study, or supporting data from experimental studies in animals. Because of the limitations of epidemiology, negative findings must also be interpreted with caution.[6]

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[6]It is important to recognize the limitations of negative epidemiological findings. A simple example reveals why this is so. Suppose a drug that causes cancer in one out of every 100 people exposed to 10 units is released for use (no one is aware of the risks). Moreover, the average time required for cancer to develop from 10 units' exposure is 30 years (not uncommon for a carcinogen). After the drug has been in use for 15 years, an epidemiologist decides to study its effects. He locates the death certificates of 20 people who took the drug, but finds little information on their dosage. Some took the drug when it was first released, others not for several years after its release. The health records, which are incomplete, reveal no excess cancer in the 20 people when compared to an appropriate control group. Is it correct to conclude that the drug is not carcinogenic?

HAZARD IDENTIFICATION: A SUMMARY

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

In some cases, all the available data may point clearly in a single direction, leaving little ambiguity about the nature of 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 a well-studied compound to have conflicting results from toxicity tests. If the tests are performed properly, positive tests 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 it is generally accepted that results in animals are and have been useful in predicting effects in humans, such notable exceptions as thalidomide have occurred. This complex issue, briefly mentioned here, must be considered for each compound examined.

The foregoing discussion of hazard evaluation was derived for exposures to a single toxic agent. Humans are rarely exposed to only one substance: 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 compounds may act independently; that is, exposure to the additional chemical(s) has no observable effect on the toxic properties of the substance. 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 produce a greater than additive (synergistic) effect; that is, exposure to chemicals A and B produces more than 3 units of disease. 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 mixtures of chemicals is complex and not standardized.

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. For the latter, at least two additional sets
of analyses must be conducted.

IV. DOSE-RESPONSE EVALUATION

INTRODUCTION

The next step in risk assessment is to estimate the dose-response relationships for the various forms of toxicity exhibited by the substance under review. Even where good epidemiological studies have been conducted, there are rarely reliable quantitative data on exposure. Hence, 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, using theories about the form of the dose-response relationship; (2) animals and humans often differ in suspectibility, if only because of differences in size and metabolism; and (3) the human population is very heterogeneous, so that 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), there are theoretical reasons to believe that effects may take place at very low dose levels; several specific mathematical models of dose-reponse relationships have been proposed. For most other biological effects, it is usually assumed that "threshold" levels exist. However, it is very difficult to use such measures to predict "safe" levels in humans. Even if it is assumed that humans and animals are, on the average, similar in intrinsic susceptibility, humans are expected to have more variable responses to toxic agents. We discuss these and other issues at length in the following subsections.

THRESHOLD EFFECTS

It is widely accepted on theoretical grounds, if not definitively proved empirically, that most biological effects of chemical substances occur only after a threshold dose is achieved. In the experimental systems described here, the threshold dose is approximated by the no-observable-effect level or NOEL.

It has also been widely accepted, at least in the process of setting public health standards, that the human population is likely to have much more variable responses to toxic agents than are the small groups of well-controlled, genetically homogeneous

animals ordinarily used in experiments. Moreover, the NOEL is itself subject to some uncertainty (e.g., how can it be known that the most serious effects of a substance have been identified?). For these reasons, standard-setting and public health agencies protect populations from substances displaying threshold effects by dividing experimental NOELs by large "safety factors." The magnitude of safety factors varies according to the nature and quality of the data from which the NOEL is derived; the seriousness of the toxic effects; the type of protection being sought (e.g., are we protecting against acute, subchronic, or chronic exposures?); and the nature of the population to be protected (e.g., the general population, or 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.

NOELs are used to calculate the Acceptable Daily Intake (ADI) for humans (which goes by other names in some circumstances) for chemical exposures. The ADI is derived by dividing the experimental NOEL, in mg/kg/day, for the toxic effect appearing at lowest dose, by one of the safety factors listed above. The ADI (or its equivalent) is thus expressed in mg/kg/day. For example, a substance with a NOEL from a chronic toxicity study of 100 mg/kg/day may be assigned an ADI of 1 mg/kg/day, for chronic human exposure. The concentration of the substance--be it pesticide, food additive, or drinking water contaminant--permitted in various media must be determined by taking into account the various uses to which the material has been or will be put, the possible routes of exposure, and the degree of human contact. The permitted concentrations, sometimes called tolerances or criteria, are assigned to ensure the ADI is not exceeded.

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

Although there may be some biological justification for assuming the need for safety factors to protect the more sensitive members of the human population, there is very little scientific support for the specific safety factors used. They are arbitrarily chosen to compensate for uncertainty and, in fact, could be seen as policy rather than scientific choices.

There is no way to determine that exposures at ADIs estimated in this fashion are without risk. The ADI represents an acceptable, low level of risk but not a guarantee of safety. Conversely, there may be a range of exposures well above the ADI, perhaps including the experimental NOEL itself, that bears no

risk to humans. The "NOEL-safety factor" approach includes no attempt to ascertain how risk changes below the range of experimentally-observed dose-response relations.

The assessment of low dose "risks" from threshold agents are discussed in   Section VI on Risk Characterization.

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 somewhat 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 is the probability of cancer, and at very low doses the risk can be extremely small (this will vary according to the potency of the carcinogen). In this respect, carcinogens are not much different from agents for which ADIs are established (i.e., the most that can be said about an ADI is that it represents a very low risk, not that it represents the condition of absolute safety).

The Carcinogenic Process

If a particular type of damage occurs to the genetic material (DNA) of even a single cell, that cell may undergo a series of changes that eventually result in the production of a tumor; however, the time required for all the necessary transitions that culminate in cancer may be a substantial portion of an animal's or human's lifetime. Carcinogens may also affect any number of the transitions from one stage of cancer development to the next. Some carcinogens appear capable only of initiating the process (these are termed "initiators"). Still others act only at later stages, the natures of which are not well known (so-called promotors may act at one or more of these later stages). And some carcinogens may act at several stages. Some scientists postulate that an arbitrarily small amount of a carcinogen, even a single molecule, could 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 would occur. Under these circumstances there is little likelihood of an absolute threshold below which there is no effect on the process (even though the effect may be exceedingly small).

This description of the carcinogenic process is still under extensive scientific scrutiny and is by no means established. However, it is by far the dominant model and it has substantial support. This multistage model has influenced the development of some of the models used for dose-response evaluation. Before discussing these models further, it is useful to review the experimental dose-response information obtained from bioassays and to discuss why models of the dose-response relation are needed.

Potency and High-to-Low Dose Extrapolation

The following example, drawn from Rodricks and Taylor,[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 been found to produce liver cancer in male rats. A typical summary of the data from such an experiment might be as follows:

Lifetime Daily Dose	Lifetime Incidence of Liver Cancer in Rats	Lifetime Probability of Liver Cancer
0 mg/kg/day	0/50	0.0
125 mg/kg/day	0/50	0.0
250 mg/kg/day	10/50	0.20
500 mg/kg/day	25/50	0.50
1000 mg/kg/day	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 (e.g., 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%) 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%; 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 contract cancer from this substance. This is an extremely high risk and obviously one

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[7]"Application of Risk Assessment to Food Safety Decision-Making," Regulatory Toxicology & Pharmacology (1983), 3:275-307.

that no one 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 it is possible to estimate the daily dose of the chemical in the human population. For the present example, assume that the exposed human population receives a dose of 1.0 mg/kg/day. It thus becomes of interest to know the risk to male rats at 1.0 mg/kg/day.

There is a great difference between the doses used experimentally and the dose of interest. The risks that would likely 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). It is thus necessary under these circumstances to rely on means other than experimentation to estimate potential risk.

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

These mathematical models are too complex for detailed exposition in this document. 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 in refining these models. Regulatory agencies currently use one-hit, multistage, and probit models, although 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 these models are applied to the data recorded earlier for the hypothetical chemical, the following estimates of lifetime risk for male rats[8] at the dose of 1.0 mg/kg/day are derived:

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[8]All risks are for a full lifetime of daily exposure. The lifetime is 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 (data drawn from Rodricks and Taylor, 1983).

Model Applied	Lifetime Risk at 1.0 mg/kg/day
One-hit	6.0×10^{-5} (one in 17,000)
Multistage	6.0×10^{-6} (one in 167,000)
Multihit	4.4×10^{-7} (one in 230,000)
Weibull	1.7×10^{-8} (one in 59 million)
Probit	1.9×10^{-10} (one in 5.2 billion)

There may be no experimental basis for deciding which estimate is closest to the truth. Nevertheless, it is possible to show that the true risk, at least to animals, is very unlikely to be higher than the highest risk predicted by the various models.

In cases where relevant data exist on biological mechanisms of action, the selection of a model should be consistent with the data. In many cases, however, such data are very limited, resulting in great uncertainty in the selection of a model for low dose extrapolation. At present, understanding of the mechanism of the process of carcinogenesis is still quite limited. Biological evidence, however, does indicate the 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.

The multistage model, which yields risk estimates either equal to or less than the one-hit model, is based on the same theory of cancer initiation. However, this model can be more flexible, allowing consideration of the data in the observable range to influence the extrapolated risk at low dose. It is also based on the multistage theory of the carcinogenic process and thus has a plausible scientific basis. EPA generally uses the linearized multistage model for low dose extrapolation because its scientific basis, although limited, is considered the strongest of the currently available extrapolation models. This model yields estimates of risk that are conservative, representing a plausible upper limit for the risk. In other words, it is unlikely that the "actual" risk is 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 certain way. The other models have more complex bases; because none is

widely used we shall not discuss them. None of the models, as currently used, incorporates a threshold dose for an exposed population.

Interspecies Extrapolation

For the majority of agents, dose-response evaluation primarily involves the analysis of tests that were performed on laboratory animals, because useful human data are generally not available. In extrapolating the results of these animal tests to humans, the doses administered to animals must be adjusted to account for differences in size and metabolic rates. Differences in metabolism may influence the validity of extrapolating from animals to man 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:

o Milligrams per kilogram body weight per day

o Milligrams per square meter of body surface area per day

o Parts per million in the air, water, or diet

o Milligrams per kilogram per lifetime.

Currently, a scientific basis for using one extrapolation method over another has not been established.

DOSE-RESPONSE EVALUATION: 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 relations and identifying experimental NOELs. NOELs can be used to establish ADIs, or can be used for the type of risk characterization described in Section VI.

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 (Section V) carcinogenic risk can be characterized (Section VI). Although the models in use yield a range of dose-response relations, it is highly likely that the projections of the more protective models will not underestimate risk, at least to experimental animals, and they may strongly overestimate it. None of the models includes a threshold. In a few cases, dose-response data are available from human epidemiology studies and may be used in lieu of animal data for low dose extrapolation.

It appears that certain classes of carcinogens do not possess the capacity to damage DNA (they are not genotoxic); in our earlier discussion of the carcinogenic process, such substances would affect only late stages in the process. 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 noncarcinogens are treated for purposes of establishing ADIs.

V. HUMAN EXPOSURE EVALUATION

Assessment of human exposure involves estimation of the number of people exposed and the magnitude, duration, and timing of their exposure. In some cases, it is fairly straightforward to measure human exposure directly, either by measuring levels of the hazardous agents in the ambient environment or by using personal monitors. In most cases, however, detailed knowledge is required of the factors that control human exposure, including those factors which 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:

- Information on the factors controlling the production of the hazardous agent and its release into the environment.

- Information on the quantities of the agent that are released, and the location and timing of release.

- Information on the factors controlling the fate of the agent in the environment after release, including factors controlling its movement, persistence, and degradation. (The degradation products may be more or less toxic than the original agent.)

- Information on factors controlling 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 of these types that is available varies greatly from case to case and is difficult to discuss in general terms. For some agents, there is fairly detailed information on the sources of release into the environment and on the factors controlling the quantities released. However, for many agents there is very limited knowledge of the factors controlling dispersion and fate after release. Measurements of transport and degradation in the complex natural environment are often difficult to conduct, so 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.

VI. RISK CHARACTERIZATION

The final step in risk assessment involves bringing together the information and analysis of the first three steps. Risk is generally characterized as follows:

1. For noncarcinogens, and for the noncarcinogenic effects of carcinogens, the margin-of-safety (MOS) is estimated by dividing the experimental NOEL by the estimated daily human 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 modelling. 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 this step can be far more complex than is indicated here, especially if problems of timing and duration of exposure are introduced (as they no doubt need to be in the present case), the MOS and the carcinogenic risk are the ultimate measures of the likelihood of human injury or disease from a given exposure or range of exposures.

The ADIs described earlier are not measures of risk; they are derived by imposing a specified safety factor (or, in the above language, a specified MOS). Our purpose here is not to specify an ADI, but to ascertain risk. There is no means available to accomplish this for noncarcinogens. The MOS is used as a surrogate for risk: as the MOS becomes larger, the risk becomes smaller. At some point, most scientists agree that the MOS is so large that human health is almost certainly not jeopardized. The magnitude of the MOS 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 ADIs.

Appendix
TOXIC EFFECTS ON ORGANS AND OTHER TARGET SYSTEMS

Appendix

INTRODUCTION

To understand the potential toxic effects of chemicals, it is useful to understand the toxic effects (i.e., measurable effects) on endpoints that are commonly observed in animals, including humans. While the following discussion is presented by organ or system, chemicals frequently affect more than one organ and can produce a variety of endpoints. Concentration of the chemical, duration of exposure, and route of exposure are three of the factors that can influence the potential toxic effect.

LIVER

A major function of the liver is metabolism--i.e., the bio-chemical conversion of one substance into another for purposes of nutrition, storage, detoxification, or excretion. The liver has multiple mechanisms for each of these processes, and interference with any of the processes can lead to a toxic effect. Chemicals that damage the liver are termed "hepatotoxic." Toxic endpoints of the liver can include lipid (e.g., fat) accumulation, jaundice, cell death (necrosis), cirrhosis, and cancer. In addition, chemicals that increase the level of metabolic enzymes, i.e., enzyme inducers, can dramatically affect the toxicity of other compounds.

The accumulation of lipids, primarily triglycerides, is related to the liver's conversion of sugars and carbohydrates into fat for storage (or vice versa for energy production during starvation). Chemicals that increase the rate of triglyceride synthesis, decrease the rate of triglyceride excretion, or both can lead to an accumulation of lipids in the liver and a concomitant decrease of triglycerides in the blood. While the effects of lipid accumulation in the liver are not known, a fatty liver is generally regarded as an indication of an injury to the organ.

Jaundice is a frequent endpoint when the excretory functions of the liver are impaired; the yellow cast of the skin is caused by the retention in the blood of the yellow bile pigments that would normally be excreted. Since blood that has absorbed compounds from the gastrointestinal tract passes through the liver before the rest of the body, the liver is a major site for the removal of nutrients and toxicants. Elimination of the absorbed toxicants can occur in the feces via the bile. In addition to

bile acting as a mechanism of excretion, bile salts aid in the absorption of nutrients that are not water soluble. Thus, impairing liver function can affect absorption of compounds. Finally, the liver is also a site of the destruction of aged red blood cells. Jaundice is an indicator of liver malfunction.

Necrosis, or cell death, can occur from multiple causes. There are many mechanisms by which toxicants can directly or indirectly inhibit required cell functions. The liver has a limited ability to regenerate destroyed cells. Chronic destruction of cells, however, may lead to cirrhosis of the liver in which the normal liver cells (hepatocytes) are replaced by altered cells and connective tissue such as collagen.

A wide variety of chemicals have been shown to cause liver cancers in laboratory animals. Exposure to vinyl chloride has been associated with liver cancers in humans. The theories and uncertainties of carcinogenesis are discussed in the main text.

As a major site of metabolism and and detoxification, the liver contains enzyme systems that biochemically alter compounds. Many of these processes facilitate excretion by making the compound more polar, i.e., highly charged (e.g., cytochrome P-450 systems) or attaching polar groups to the compound (e.g., glutathione, glycuronyl, or sulfo-transferases). The speed at which this occurs depends on the amount of enzyme present; the amount of enzyme can be increased by exposure to certain chemicals called inducers. If a nonmetabolized compound is toxic, exposure to an inducer may decrease the toxic effect by increasing the rate at which the compound is metabolized. If the compound needs to be metabolized to be toxic, however, exposure to an inducer may increase the toxic effect by increasing the rate of its metabolism.

KIDNEY

As an organ whose major function is the elimination of toxicants and other waste products, the kidney can be considered a complex, elaborate filter. The kidney concentrates wastes for elimination and retains nutrients and water that are useful to the body. The kidney can metabolize and detoxify some of the same compounds as the liver, although the rate of metabolism is usually slower. Compounds that injure the kidney are called renal toxicants. Some renal toxicants may cause cell death (necrosis) or cancer. In addition, the kidney produces chemicals necessary for homeostasis (maintenance of the body's balance of functions) and responds to the sympathetic nervous system. To efficiently remove the body's waste, the kidneys must process

large volumes of blood. Thus, the first level of susceptibility of the kidney is that which changes the flow of fluids. This change can be mechanical--e.g., kidney stones or puncturing vesicles--or chemicals that dilate or constrict the passages.

The complexity of the kidney's filtering function makes it susceptible to a number of toxicants. Although some of the filtering requires no energy or special enzymes since the flow is from high to low concentrations, much of the selection is to a higher concentration than in the blood and is performed by enzymes that may be affected by chemicals. Excessive elimination of water, salts, or other nutrients can be as harmful as failure to eliminate wastes. Furthermore, because the kidneys concentrate some toxicants, the effective dose of toxicants to the kidneys may be higher than that for the rest of the body. Toxicants that cause necrosis can also impair renal function. Failure of the kidneys to filter properly is frequently detected by an increase in wastes in the blood or an increase in nutrients in the urine.

The ability of the kidney to metabolize compounds has not been studied as extensively as has metabolism in the liver. The presence of inducible metabolic enzyme systems is known. Other specific metabolic functions occur in the kidney. Finally, because the kidney produces compounds that are necessary for other body functions, damage to the kidney may affect other organ systems.

REPRODUCTIVE SYSTEM

Reproductive toxicology involves at least three organisms (both male and female parents and their offspring) and consists of many steps and stages. Toxic effects to the reproductive system can be classified into three general endpoints: impaired ability to conceive, failure of the conceptus to survive, and production of abnormal offspring.

Problems with conception usually result from impaired production of the sperm or egg. The formation of sperm (spermatogenesis) is continuous in the male and requires a series of steps. Chemicals that interfere with these steps may prevent sperm production and cause sterility, reduce sperm production, or result in abnormal sperm that have reduced capacity to fertilize. Although in mammals all eggs are formed before birth, their final maturation occurs in cycles after puberty. Chemicals, e.g., contraceptives, can impede this process. Mature sperm and egg, as well as proper biochemical and physiological conditions within the body, are required for fertilization.

Viability of the conceptus depends on a series of steps, including implantation and development of the amniotic sac and placenta. Death of the conceptus, whether at the early embryonic stage or later fetal stage, can be caused by a variety of factors including chemicals. Such chemicals are labeled "embryotoxic" and "fetotoxic," respectively.

Chemicals that cause defects in development and result in abnormal offspring are called "teratogens." Defects range from abnormal skeletal or muscle structure and mental retardation, to metabolic malfunctions, to subtle malfunctions that may not be noticed during a normal life.

Functionally, for the developing mammal to be exposed, the chemical must pass through two barriers: the mother and the placenta. If a given dose of a compound is sufficiently toxic to kill the mother, resultant toxic effects on the offspring will not be observed. Although this statement may seem trivial, its converse is an important principle in teratogenesis. The more dangerous teratogens are those which affect the developing organism at concentrations that are significantly lower than those that affect the adult mother.

Although the placenta was once thought to be a rather strong barrier, many chemicals have been found to cross to the conceptus. Depending on the compound, the final concentration may be higher in the mother, higher in the conceptus, or equal in mother and conceptus. Moreover, the placenta is not inert but is capable of metabolizing some chemicals into either more or less toxic substances. Metabolism may also affect the flow of compound across the placenta.

Timing has two critical aspects in teratogenesis: timing of the dose during development and parallel timing of developing systems. Time of exposure to the potential teratogen may not only determine which developing system is affected but also whether the compound will have any effect at all. For each developing system there is a critical period, usually between three and twelve weeks in the human, during which the system is particularly sensitive to chemically induced abnormal development. Although terata may form after this period, the abnormalities are usually less severe.

The second aspect of timing involves the relative rate of development of each of the organ systems. To produce a well-formed offspring, development must be well orchestrated. As with a symphony, the pace must be parallel in all sections. Nerves cannot attach to muscles that are not present; cleft palate in laboratory animals is frequently caused by events occurring out

of sequence. If all the developing systems were equally retarded, the result might be an immature, but not malformed fetus.

LUNGS

The major function of the lungs is to exchange oxygen and carbon dioxide between blood and air. This same mechanism can facilitate entry and exit of other compounds from the body. In addition, the lungs have the ability to alter some chemicals metabolically. Damage to the lung can range from irritation and constriction, to cell death (necrosis), edema, or fibrosis, to cancer.

The air not only contains a variety of gases but also small suspended particulates and liquid aerosols. The fate and, therefore, potential to cause damage, for each physical state depends on the size and composition of the inhaled substance. An analogy is often drawn between the airways of the respiratory passages and the structure of a tree. In both, the starting point has a large diameter and branches into more numerous but increasingly smaller appendages. Given the size of the passage and the fact that large particles fall out of suspension faster, larger inhaled particulates and droplets will generally deposit in the upper respiratory tract. Deposition is also affected by the breathing pattern--for example, how fast and how deep.

The lung contains other mechanisms for handling inhaled substances including secretions, the mucociliary escalator, and macrophages. Secretions, including mucus, can facilitate transport of compounds across the lungs, between the air and blood. The mucociliary escalator consists of mucus and hairlike projections in the upper respiratory passages. The latter move so that particles that have been deposited are transported up the passage until they can be swallowed. Substances that either affect the mucus or inhibit the cilia movement can impair this process. Macrophages are a type of mobile cell that can engulf particles.

Lungs facilitate exchange in both directions between air and blood; thus, they can be equally efficient in absorption or excretion from the body. Whether a given substance is concentrated in the blood or in the lung air or is at equal concentrations on both sides depends on several factors, including its solubility in water and ability to be bound to proteins in the blood. Furthermore, lungs are able to metabolize some chemicals. These changes may alter the chemical properties and, therefore, the transport of the chemical.

Chemicals that irritate the lung can lead to discomfort. Although the effects of exposure to irritants are usually reversible, chronic exposure may lead to permanent cell damage. The normal, necessary exchange of gases across the lung can be impaired by compounds that constrict the respiratory passages, affect secretions or other normal functions, or physically remain in the lung. Substances that cause necrosis, edema (excessive fluid retention), or fibrosis (a change in cell type and composition) will impair lung function. Exposure to some substances, such as cigarette smoke, asbestos, and arsenic, can lead to impaired lung function and cancer.

SKIN

Skin is a barrier between the internal organism and the external environment. It prevents loss of body fluids, regulates body temperature, and prevents entry of many substances. However, the skin is a route of entry for some toxicants. Dermal toxicants can cause irritation, sensitization, pigmentation changes, chloracne, ulcerations, and cancer.

The skin can also be a major route of entry for other substances--for example, some pesticides and solvents. Moreover, abrasions or cuts on the skin can compromise the barrier. Compounds that are absorbed through the skin may affect other systems--for example, organophosphate pesticides that affect the nervous system. Similarly, compounds that enter by other routes may affect the skin--for example, the oral ingestion of arsenic causes dermal changes.

Irritation, rashes, and itching are common toxic reactions to dermal exposures. Chemical sensitizers may cause an allergic reaction that becomes more severe with continued exposure to light. Folliculitis (damage to the hair follicles) and acne are other common skin disorders. Chloracne is a particular form of acne that is often caused by exposure to chlorinated hydrocarbons. Compounds can change skin pigmentation. Skin keratoses (hardening or scaling) or ulcers are additional toxic responses. Skin cancer may be caused by dermal contact with some agents or systemic administration of others.

CENTRAL NERVOUS SYSTEM

The major function of the central nervous system (CNS) is communication. Control of reflexes, movement, sensory information, autonomic functions (e.g., breathing), and intelligence are

controlled by the CNS. These functions can be impaired by toxicants. Damage to the nervous system can occur in the brain or other nerve cell bodies, to nerve processes that extend through the body, to the myelin sheaths that cover these processes, and at the nerve-nerve or nerve-muscle junctions. Damage to nerve cell functions are often called "neuropathies."

As in other cells, damage to the cell body of a neuron (nerve cell) can result in impaired function or death. The brain is partially protected by the blood-brain barrier. Like other physiological barriers, this one has proven more permeable than originally thought, although it does block or reduce the passage of some substances to the brain. In contrast, certain substances, such as organic mercury, have been shown to concentrate in the CNS.

Axons are long processes that conduct impulses from the nerve cell body; they can span much of the length of an animal. Severing the axon can destroy transmission of signals along the nerve. Because electrical signals are transmitted by charged elements (ions), chemicals that change the permeability of the cell membrane to ions can also impair transmission of the signal.

Myelin is the insulating cover of axons. Special cells, called Schwann cells, form myelin by wrapping themselves in many layers around the axons. Chemicals can either destroy the myelin or decrease its amount, both of which decrease the insulation and impair signal transmission. Furthermore, demyelination of nerves can cause a degeneration of the axon. These effects take time to occur, even if damage is caused by a single exposure. Thus, the effect may be delayed and not immediately associated with the exposure.

Transmission of signals between nerves or from a nerve to a muscle occurs across a space or junction. Chemical compounds that are stored in vesicles at the nerve endings carry the signal across the junctions. Exposure to chemicals may accelerate or inhibit release of these vesicles, mimic the compounds that are released from the vesicles, or block the receptors that react to release of the compounds. Any of these responses will distort the signal.

Subjective or behavior neurological toxicology may be the most difficult toxicological effects to assess. While generally accepted that exposure to some chemicals can cause headaches, fatigue, or irritability, it is difficult to determine whether such symptoms are caused by chemical exposure, lack of sleep, depression, or other factors. Although these symptoms may be mild and difficult to assess, they are frequently an early warning of exposure to a toxicant.

Behavioral changes are often caused by damage to the nervous system. In laboratory animals, such damage may be as precise and fatal as failure of pups to nurse. Mental retardation and learning disabilities are other measurable behavioral changes. Chemical alteration of behavior is the basis for psychological drug therapy. Thus, although they are difficult to assess, behavioral changes should not be ignored.

BLOOD

Transport of oxygen, carbon dioxide, and other materials is the major function of blood. The hematopoietic system, which includes organs and tissues that produce, transport, and filter blood, interacts with the cells of all other systems. Toxicity can occur to developing blood cells, existing cells, or the hematopoietic organs.

In the human being and other mammals, blood cells are formed in bone marrow; the three major types of blood cells are formed by branches from a common precursor cell. Red blood cells contain hemoglobin and transport oxygen and carbon dioxide. White blood cells function as part of the immune system. Platelets are necessary for blood clotting. Chemicals toxic to bone marrow can affect blood formation. Depending on the stage and cell affected, any or all of the major blood cells may be decreased in number. Abnormal increases in production of certain blood cells are also possible, as in leukemia (excess white cells).

Blood plasma contains a number of proteins, ions, and other compounds. Changes in the chemical composition of blood may indicate a toxic response. Furthermore, some chemicals bind to plasma proteins. Changes in plasma protein composition could affect the effective concentration of a toxicant.

The normal function of the hemoglobin in circulating red blood cells is critical to the transport of oxygen to and carbon dioxide from all cells in the body. Reduced oxygen supply can be very detrimental; the effects resulting from oxygen deprivation vary with the site of action. Chemicals can affect hemoglobin by chemically oxidizing the heme group (causing methemoglobin) or by denaturing the hemoglobin (which may lead to the formation of Heinz bodies).

Two other hematopoietic organs that may be affected are the spleen and heart. The former removes old or damaged red blood cells from circulation. The rate and efficiency of the heart's pumping action can be altered by many causes. Chemicals that

constrict or dilate the blood vesicles can also affect circulatory function.

IMMUNE SYSTEM

Recognition and protection against foreign substances in the body is handled by the immune system. Rapid advances are being made in immunology research; therefore, current knowledge may soon be obsolete. Three types of cells (macrophages, B lymphocytes, and T lymphocytes) are part of the body's immune response. These cells interact at the peripheral lymphoid organs (lymph nodes, spleen, and tonsils). Exposure to chemicals may activate or supress the immune system.

The cells involved in the immune system are formed in bone marrow; hence, chemicals that affect bone marrow may impair immune function. One type of cell engulfs foreign matter, especially bacterial and viruses, by phagocytosis. Another type produces the five classes of antibodies. A third type produces polypeptides, such as interferon, that are important for some immune responses; this type of cell is also involved in cell-mediated immunity, such as contact dermatitis, and may partially regulate the function of antibody-producing cells.

Chemicals may stimulate immune responses by several mechanisms including acting as allergens or by stimulating production of interferon. Chemicals may also suppress immune response; immunosuppressants result in an increased susceptibility to infection and may result in an increased susceptibility to some forms of cancer.

GENETIC TOXICOLOGY

The integrity of genetic material (DNA) in all cells is critical to cell function and may be affected by some toxic agents. Damage may take several forms: alteration in the chemical composition of DNA, change in the physical structure of DNA, or addition or deletion of chromosomes. Effects of genetic toxicity can range from no observable effect to cancer. Genetic toxicity has become a popular endpoint for toxicity testing because test results can be obtained relatively rapidly and inexpensively.

Genetic damage can occur by many mechanisms; the results are generally classified in three groups: mutations, clastogenic events, and aneuploidy. Mutagens are substances that change the

chemical structure of DNA. Since DNA is "read" to provide information necessary for cell function and proliferation, mutations may cause a misreading, leading to cell damage. Clastogens cause a break in one or more strands of DNA and a physical rearrangement of its parts. Depending on where the break occurs, clastogens may affect cell proliferation or the production of cell proteins. Aneuploidy is an addition or deletion of the number of chromosomes; a commonly known aneuploidy is Down's syndrome (Mongolism) in which there is an extra chromosome. Aneuploidy is often caused by chemicals that affect cell division.

Genetic toxicology is often considered with carcinogenicity since many carcinogens are mutagens and testing for mutagenicity is easier than testing for carcinogenicity. Genetic toxicants, however, can have many effects. Much of the DNA in cells is quiescent. Since skin cells do not produce hemoglobin, there will be little damage if instructions for producing hemoglobin are damaged in a skin cell. Such events are called silent mutations. Genetic damage can alter cell proteins and, therefore, normal functioning of cells. Improper cell function may lead to cell death or cancer. Finally, if the damage is in the reproductive system, genetic toxicants can cause reproductive failure or abnormal offspring.

A variety of genetic toxicology tests have been developed in recent years. Many are performed in vitro (outside the whole animal--e.g., the Ames mutagenicity assay) and use cells grown in liquids; some are performed in vivo (within the animal). These tests are often referred to as short-term testing and require less time, and therefore, less money. Typically, short-term tests take days to months as contrasted with several years required for carcinogenicity testing.

J. ASSESSING RISK

INTRODUCTION TO PRINCIPLES USED IN RISK ASSESSMENT CASE STUDY

Prepared by C. Richard Cothern
Health Effects Branch
Criteria and Standards Division
EPA Office of Drinking Water
Washington, DC 20460

RISK

- SUBJECTIVE
- NOT A RISK FREE WORLD
- UNCERTAINTY AND COMPLEXITY
- PROBABILISTIC
- BENCHMARKS
- PRODUCT OF PROBABILITY AND CONSEQUENCE

RISK ESTIMATION

- **RANGE-WANT TO NARROW**
- **NOT NEW**
  - **QC**
  - **INSURANCE**
  - **MEDICAL COUNSELING**
- **NEW PROBLEMS**
  - **RARE EVENTS**
  - **PERCEPTION OF VALUE**
  - **LARGE UNCERTAINTIES**

WHAT ARE THE COMPONENTS OF RISK ASSESSMENT?

Hazard Identification

Dose-Response Evaluation

Human Exposure Evaluation

Risk Characterization

RISK ASSESSMENT
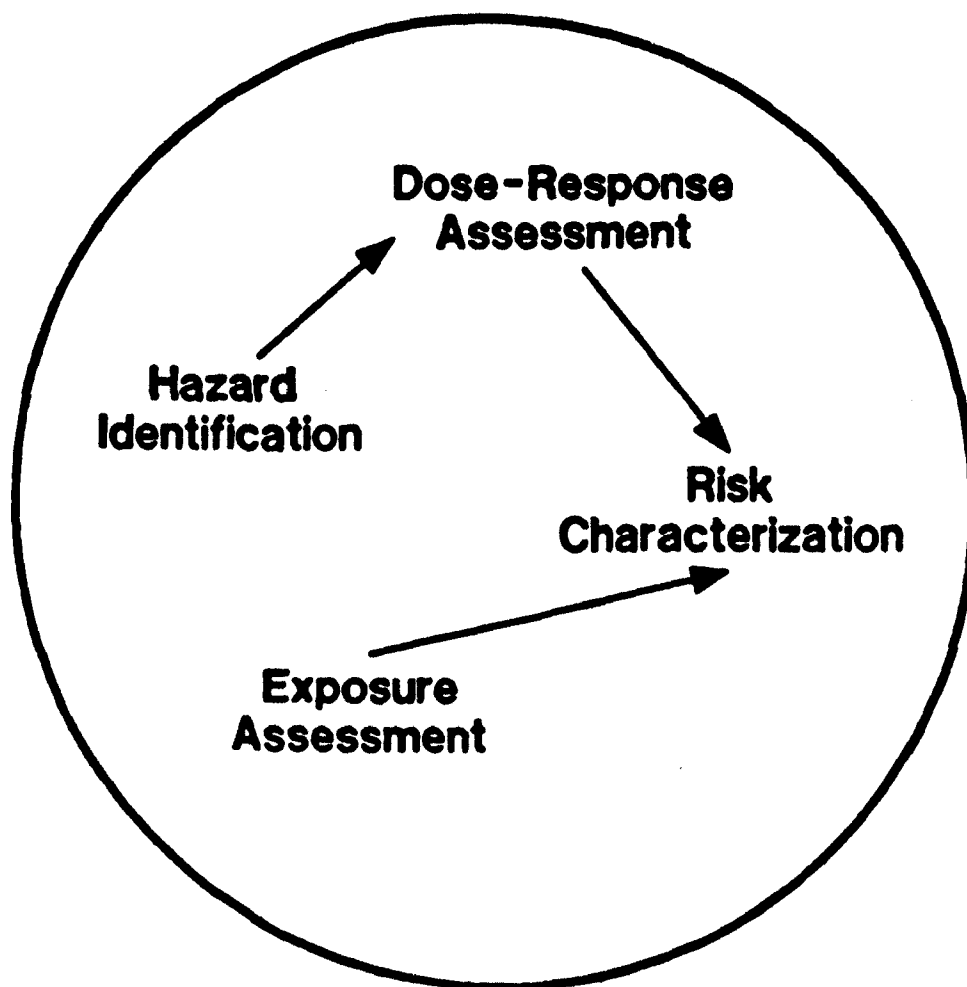
HAZARD IDENTIFICATION

- Review and analyze toxicity data

- Weigh the evidence that a substance causes various toxic effects

- Evaluate whether toxic effects in one setting will occur in other settings

RISK ASSESSMENT ISSUES

Hazard Identification

Use of animal data

Negative epidemiological studies

SOURCES OF TOXICITY DATA

Human Studies

Case reports

Epidemiologic studies
  Geographical
  Temporal

Animal Studies

General toxicity studies
- Acute
- Chronic

Specialized toxicity studies
- Teratology
- Mutagenicity

Test Tube Studies

- Microbiological
- Mammalian

FORMS OF HUMAN EXPOSURE

Inhalation
Ingestion
Skin Contact

HUMAN EXPOSURE EVALUATION

- How may people be exposed?
- Through which routes?
- Who is exposed?
- What is the magnitude, duration, and timing of the exposure?

RISK ASSESSMENT ISSUES

Hazard
Identification

Use of animal data

Negative epidemio-
logical studies

Dose-Response
Evaluation

Extrapolating from high
dose to low dose

Extrapolating from
animals to humans

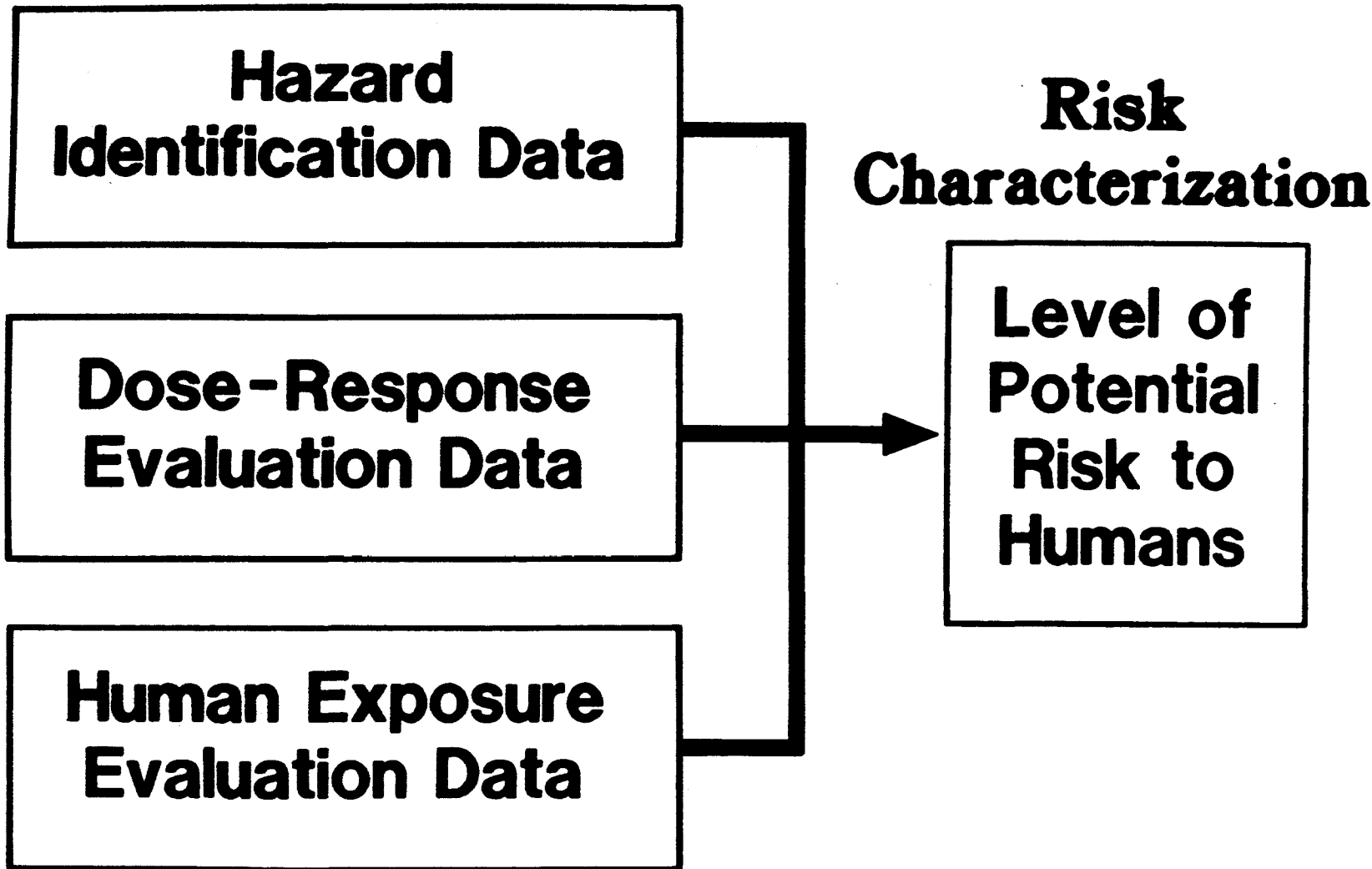# DOSE-RESPONSE EVALUATION

Performed to estimate the incidence of the adverse effect as a function of the magnitude of human exposure to a substance
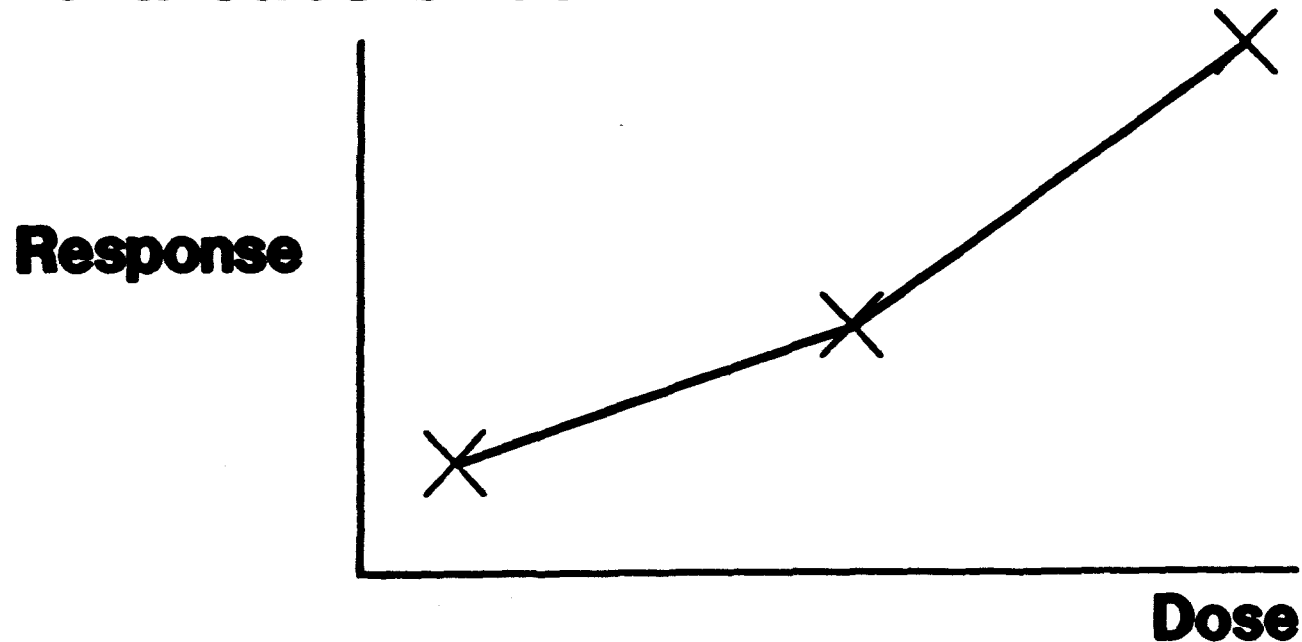
DOSE-RESPONSE CURVE
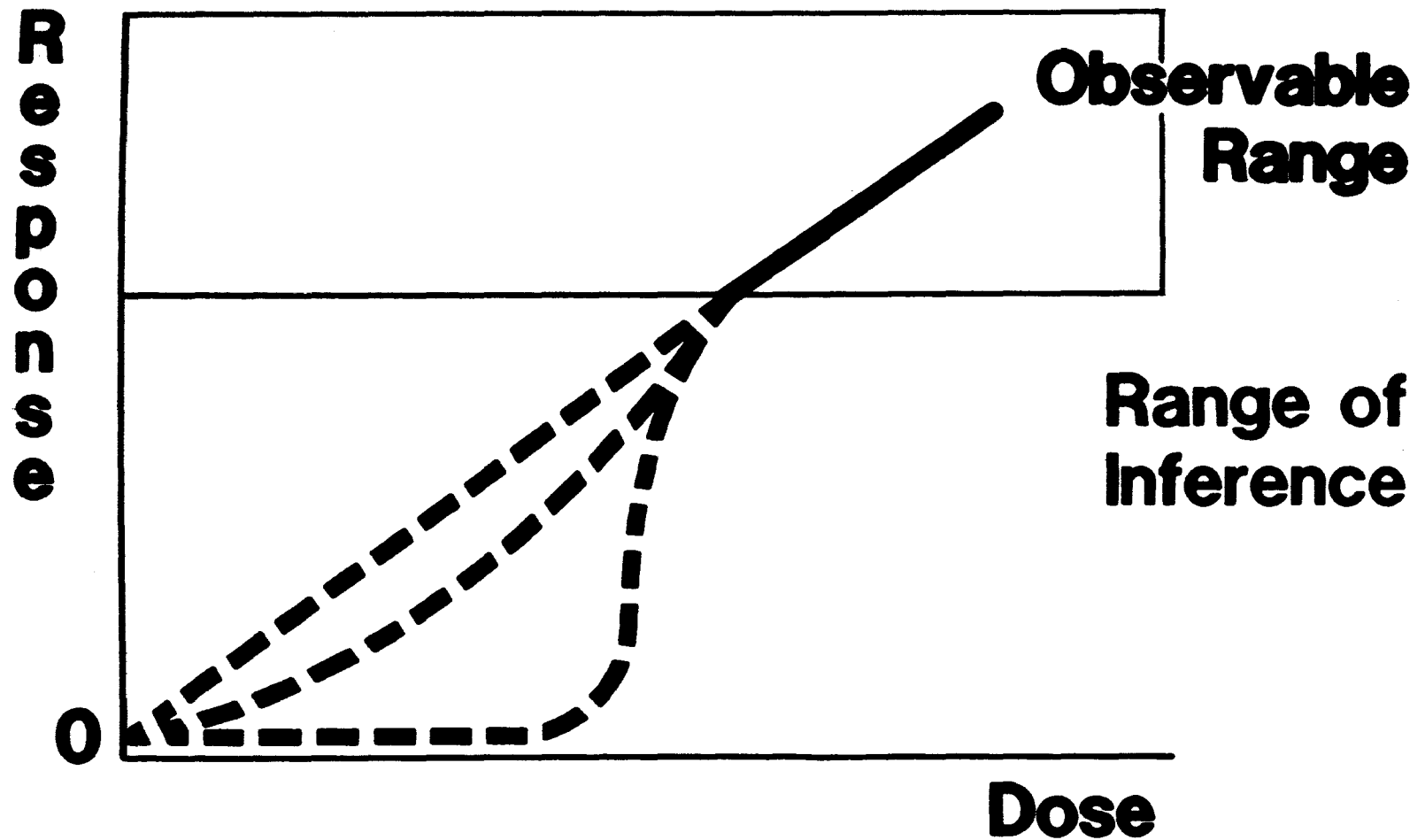
ESTIMATED NUMBER OF GROUNDWATER SYSTEMS IN EACH SIZE CATEGORY WITH TRICHLOROETHYLENE IN THE INDICATED CONCENTRATION RANGES (MICROGRAMS / LITER)

System Size (population served)	No. of Systems in U.S.	Estimated Number of Systems with Concentrations (micrograms / liter) of:												
		<0.5a	0.5-5	>5-10	>10-20	>20-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-100	>100
25-100	19125	18506	465	26	52	0	26	0	26	0	0	0	0	26
101-500	15674	15166	381	21	42	0	21	0	21	0	0	0	0	21
501-1,000	4877	4719	118	7	13	0	7	0	7	0	0	0	0	7
1,001-2,500	4400	4257	107	6	12	0	6	0	6	0	0	0	0	6
2,501-3,300	891	862	22	1	2	0	1	0	1	0	0	0	0	1
3,301-5,000	1065	1031	26	1	3	0	1	0	1	0	0	0	0	1
5,001-10,000	1168	1130	28	2	3	0	2	0	2	0	0	0	0	2
10,001-25,000	835	775	34	11	4	0	0	8	0	0	4	0	0	0
25,001-50,000	290	269	12	4	1	0	0	3	0	0	1	0	0	0
50,001-75,000	64	59	3	1	0	0	0	1	0	0	0	0	0	0
75,001-100,000	14	13	1	0	0	0	0	0	0	0	0	0	0	0
>100,000	55	41	14	0	0	0	0	0	0	0	0	0	0	0
TOTAL	48458	46828	1211	80	132	0	64	12	64	0	5	0	0	64

TRICHLOROETHYLENE

Hepatocellular Carcinomas in Male Mice

Animal dose (mg/kg/day)	Human Equivalent (mg/kg/day)	Animals Affected/Total
0	0	1/20
1530	56.3	26/50
2700	112.6	31/48

5 days/wk - multiply by 5/7

1 1/2 yr experiment - multiply by 1.5/2

bodysize - multiply by $(0.033/70)^{1/3}$

MODEL	PROBABILITY P(d) OF A RESPONSE AT DOSE d	LOW-DOSE BEHAVIOR		
		LINEAR	SUB LINEAR	SUPRA LINEAR
PROBIT	$(2\pi)^{-1/2}\int_{-\infty}^{\alpha+\beta\log d}\exp(-u^2/2)du$ ($\beta>0$)	—	$\beta>0$	—
LOGIT	$\left[1+\exp(-\alpha-\beta\log d)\right]^{-1}$ ($\beta>0$)	$\beta=1$	$\beta>1$	$\beta<1$
WEIBULL	$1-\exp(-\lambda d^m)$ ($\lambda, m>0$)	$m=1$	$m>1$	$m<1$
ONE-HIT	$1-\exp(-\lambda d)$ $d>0$	$\lambda>0$	—	—
MULTI-STAGE	$1-\exp(-\sum_{i=1}^{k}\beta_i d^i)$ ($\beta_1\geq 0$)	$\beta_1>0$	$\beta_1=0$	—
MULTI-HIT	$\int_0^{\beta d}\frac{(u^{k-1}e^{-u})}{\Gamma(k)}du$	$k=1$	$k>1$	$k<1$

TRICHLOROETHYLENE
(ingestion)

WEIBULL

LOGIT

MULTISTAGE

PROBIT

LIFETIME RISK/PERSON EXPOSED
(VIA INGESTION, INHALATION AND DERMAL ROUTES ASSUMING INGESTION =
INHALATION AND DERMAL ROUTES ASSUMING INGESTION =
INHALATION PLUS DERMAL)

CONCENTRATION IN DRINKING WATER (micrograms/liter)

148
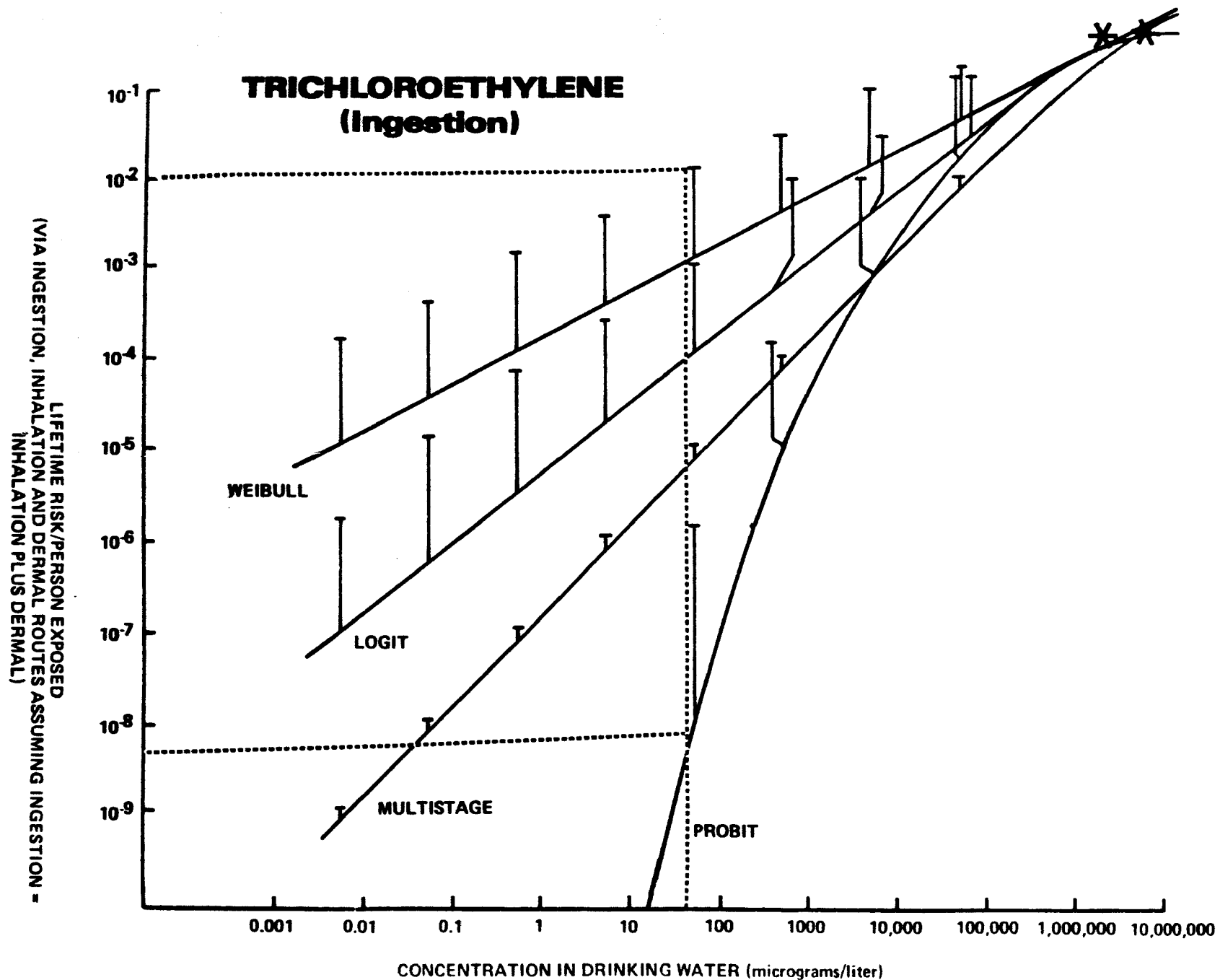
TRICHLOROETHYLENE

Drinking Water Concentration (μ/L)	Number of People Served	Lifetime Individual Risk Range		Lifetime Population Risk	
0.25	1.9×10^8	$<10^{-10}$	6×10^{-4}	$<1-$	100,000
2.75	2.3×10^7	$<10^{-10}$	1×10^{-3}	$<1-$	20,000
7.5	4.3×10^5	$<10^{-10}$	2×10^{-3}	$<1-$	800
15	2.1×10^5	$<10^{-10}$	6×10^{-3}	$<1-$	1,200
35	7.4×10^5	7×10^{-8}	1×10^{-2}	$<1-$	7,000
45	2.6×10^5	3×10^{-7}	1×10^{-2}	$<1-$	3,000
55	4.2×10^4	4×10^{-7}	1×10^{-2}	$<1-$	400
75	1.3×10^5	6×10^{-7}	2×10^{-2}	$<1-$	2,000
100	4.2×10^4	1×10^{-6}	2×10^{-2}	$<1-$	800
				$<1-$	100,000

CONTAMINANT	ANNUAL POPULATION RISK RANGE
Cigarette Smoke	
Active	100,000
Passive	2,000-5,000
Radon	
Soil	5,000-20,000
Water	50-2,000
Radium-226	3-60
Uranium-Nat	1-10
Strontium-90	1-2
1,2 Dichloropropane	$<10^{-8}$ - 100
Alachlor	$<10^{-8}$ - 1
Asbestos	5×10^{-4} - 1
Chloroform	$<10^{-4}$ - 10
Trichloroethylene	$<10^{-5}$ - 1,000

VINYL CHLORIDE (Ingestion)

CONCENTRATION IN DRINKING WATER (micrograms/liter)

LIFETIME RISK/PERSON EXPOSED (VIA INGESTION, INHALATION AND DERMAL ROUTES ASSUMING INGESTION = INHALATION PLUS DERMAL)

WEIBULL

MULTISTAGE

LOGIT

PROBIT

152

**VINYL CHLORIDE
(Ingestion-Maltoni)**

CONCENTRATION IN DRINKING WATER (micrograms/liter)

LIFETIME RISK/PERSON EXPOSED
(VIA INGESTION, INHALATION, INHALATION AND DERMAL ROUTES ASSUMING INGESTION =
INHALATION PLUS DERMAL)

WEIBULL

LOGIT

MULTISTAGE

PROBIT

153

Threshold

Non-Threshold

No Effect

Organ Damage

Cancer

154

RISK CHARACTERIZATION

327 per 1,000,000 exposed people will die from lifetime exposure to Chemical A.

RISK CHARACTERIZATION

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.

RISK CHARACTERIZATION

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.

DATA LIMITATION	SCIENCE POLICY OPTIONS	COMMENTS
ANIMAL ENDPOINTS MAY NOT BE FOUND IN HUMANS	• ASSUME THAT THERE IS CANCER IN ANIMALS, WILL HAVE CANCER FOR SOME HUMAN ENDPOINTS • ASSUME WILL NOT OCCUR IN HUMANS • ASSUME SAME ENDPOINTS	• ZYMBAL GLAND • LIVER • MULTITUDE OF ENDPOINTS - e.g., LEAD

DATA LIMITATION	SCIENCE POLICY OPTIONS	COMMENTS
SYNERGISM AND ANTAGONISM	• ASSUME THAT NEITHER EXISTS AND THAT EFFECTS ADD LINEARLY • USE A SAFETY FACTOR	• ASBESTOS, RADON AND CIGARETTE SMOKE • FEW MORE THAN 10, MOST 2 OR LESS • COST OF TESTING

COMPARATIVE RISKS
OF DEATH

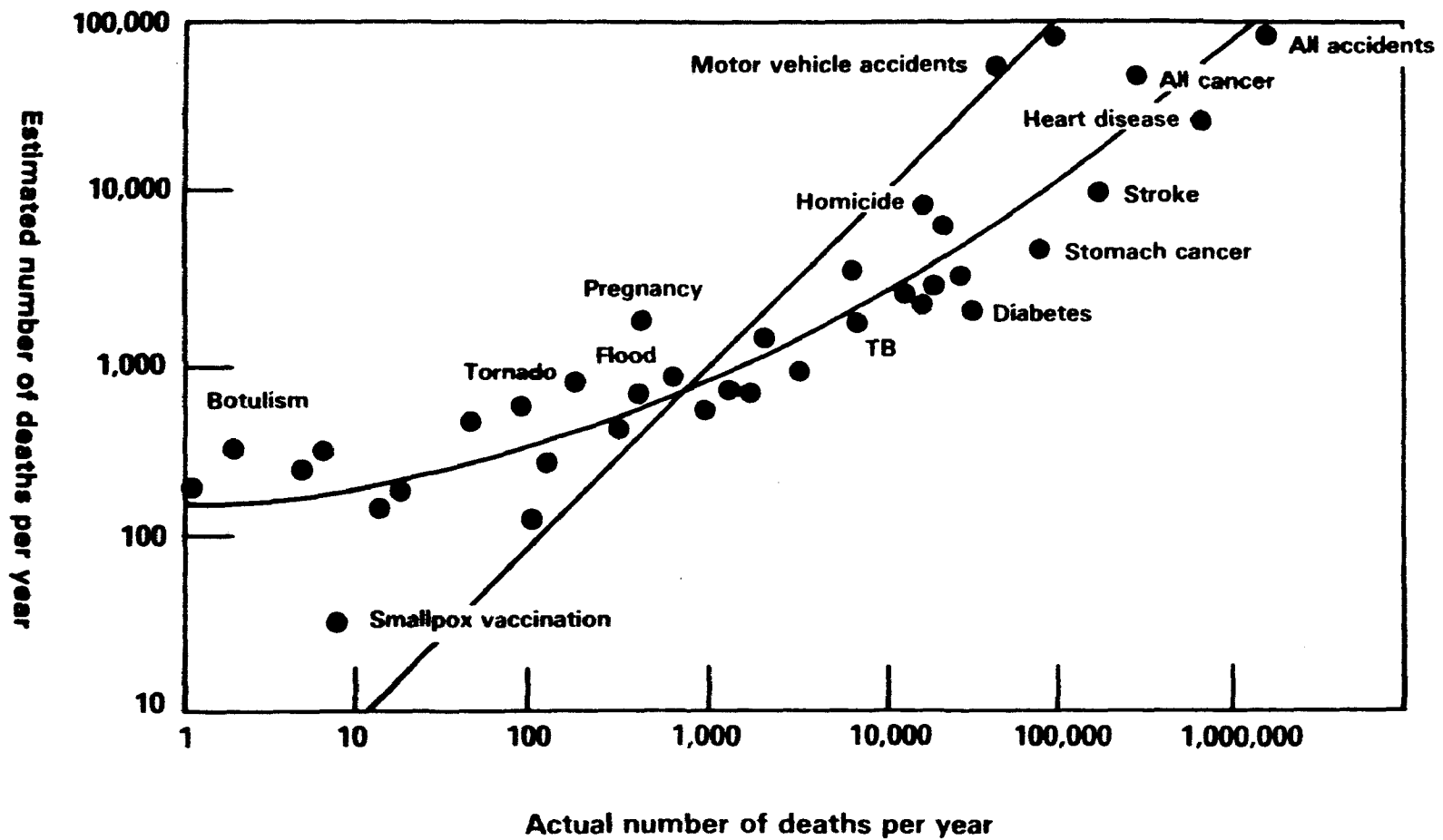|	Number of Deaths / Year	Lifetime Risks
Motor vehicle accidents	46,000	1/65
Home accidents	25,000	1/130
Lung cancer deaths in smokers	80,000	1/12

ACTIVITIES THAT INCREASE CHANCE OF DEATH BY ONE IN A MILLION YEARLY	CAUSE OF DEATH
SMOKING 1.4 CIGARETTES	CANCER, HEART DISEASE
SPENDING 1 HR. IN A COAL MINE	BLACK LUNG DISEASE
SPENDING 3 HRS. IN A COAL MINE	ACCIDENT
TRAVELING 10 MILES BY BICYCLE	ACCIDENT
TRAVELING 300 MILES BY CAR	ACCIDENT
FLYING 1000 MILES BY JET	ACCIDENT
FLYING 6000 MILES BY JET	CANCER FROM COSMIC RADIATION
LIVING 2 MONTHS IN DENVER	CANCER FROM COSMIC RADIATION
LIVING 2 MONTHS IN AVERAGE STONE OR BRICK BUILDING	CANCER FROM NATURAL RADIO-ACTIVITY
ONE CHEST X-RAY TAKEN IN A GOOD HOSPITAL	CANCER FROM RADIATION
LIVING 2 MONTHS WITH A CIGARETTE SMOKER	CANCER, HEART DISEASE
DRINKING 30 12-OUNCE CANS OF DIET SODA	CANCER FROM SACCHARIN
LIVING FIVE YEARS AT SITE BOUNDARY OF A TYPICAL NUCLEAR POWER PLANT IN THE OPEN	CANCER FROM RADIATION
DRINKING 1000 24-OZ SOFT DRINKS FROM RECENTLY BANNED PLASTIC BOTTLES	CANCER FROM ACRYLONITRILE MONOMER
EATING 100 CHARCOAL BROILED STEAKS	CANCER FROM BENZOPYRENE

SOURCE: "ANALYZING THE DAILY RISKS OF LIFE," BY RICHARD WILSON, TECHNOLOGY REVIEW, FEBRUARY 1979. BECAUSE OF THE NATURE OF THE DATA ON WHICH THEY ARE BASED, SOME OF THESE EXAMPLES ARE SUBJECT TO CONSIDERABLE UNCERTAINTY. IN A FEW CASES INVOLVING PROBABLY AS MUCH AS SEVERAL FACTORS OF 10.

CONTAMINANT	ESTIMATED NUMBER OF DEATHS IN A LIFE-TIME IN THE U.S. DUE TO CONCENTRATIONS IN THE DRINKING WATER
RADIUM	500 - 1000
URANIUM	500 - 1000
RADON	6000-100,000
CHLOROFORM	50,000 - 200,000
CARBON TETRACHLORIDE	100 - 300
TRICHLOROETHYLENE	20 - 150
TETRACHLOROETHYLENE	20 - 100
BENZENE	10 - 200
VINYL CHLORIDE	0 - 200

General Problems in Communicating Risk Assessment Information to Regulatory Decisionmakers and Some Possible Solutions.

COMMUNICATION PROBLEM	POTENTIAL SOLUTION

● LANGUAGE
 	
● COMPLEX NATURE OF RISK
ASSESSMENT INFORMATION
 	
● LACK OF UNDERSTANDING
OF CONCEPTS SUCH AS
UNCERTAINTY AND PROBABILITY
	● USE WORDS WITH POSITIVE CONNOTATION
	
	● MORE CLARITY AND REALITY IN SCIENTIFIC
	AND TECHNICAL INFORMATION PRESENTED
	(e.g., USE UNCERTAINTY)
	
	● EDUCATION
	    – SCHOOLS
	    – NEWS MEDIA
	    – USE EVERYDAY EXAMPLES

163

RISK ASSESSMENT

Dose-Response Assessment

Hazard Identification

Risk Characterization

Exposure Assessment

165

RISK ASSESSMENT

RISK MANAGEMENT

Dose-Response Assessment

Hazard Identification

Risk Characterization

Exposure Assessment

Regulatory Decision

Control Options

Non-Risk Analyses

NON-RISK ANALYSES

R_L = .42P^{-.51}

R_L = .015/√P̄

- ■ REGULATED OR REGULATION UNDER STUDY
- △ DECISION NOT TO REGULATE
- ◇ FATAL ACCIDENTS

LOG OF LIFE TIME RISK (R_L)

LOG OF POPULATION (P)

168

ACTION

INDIVIDUAL LIFETIME
RISK ROLE

LIFETIME POPULATION
RISK IF ENTIRE
U.S. IS EXPOSED

RADON

10^{-4} ———— 20,000

CHLOROFORM,
CARBONTETRACHLORIDE,
AND MANY ORGANICS
AND INORGANICS

DECISION

RADIUM   URANIUM

10^{-6} ———— 200

DEMINIMUS

OTHER
ORGANICS
AND
INORGANICS

169

Activities or Types of Exposure that Will Reduce One's Life Expectancy by Eight Minutes Due to the Increased Likelihood of Having Cancer

- Smoking 1.4 cigarettes

- Living two months with a cigarette smoker

- One x-ray (in a good hospital)

- Eating 100 charcoal-broiled steaks

- Eating 40 tablespoons of peanut butter

- Drinking 30 12-oz soft drinks from recently banned plastic bottles

- Living 20 years near a polyvinyl chloride plant

- Living 15 years within 30 mi of a nuclear power plant

(From Wilson, R., "A Rational Approach to Reducing Cancer Risk". New York Times, July 7, 1978)

Common Daily Probabilistic Choices

Category	Probability
Weatherman (forecast probabilities	10% 80%
Bus or Train Being Late 5 minutes 10 minutes 20 minutes 30 minutes	 50% 40% 5% 1%
Airplane Takeoff or Arrival Being Late	 50%
Medical Probabilities Inheritable traits (color blindness, Huntington's Chorea, diabetes) Heart trouble Breast cancer Lung cancer Smoker (3 packs a day) Non--smoker	 25% 40% 20% 60% 5%
Alarm Clock Failure	1/365
Car Failing to Start	1/365
Gambling Poker Roulette Dice Lotteries (winning jackpot)	 1/52 1/38 1/6 1×10^6

RISK FACTORS

VOLITION	VOLUNTARY	— INVOLUNTARY
SEVERITY	ORDINARY	— CATASTROPHIC
ORIGIN	NATURAL	— MAN-MADE
EFFECT MANIFESTATION	IMMEDIATE	— DELAYED
EXPOSURE PATTERN	CONTINUOUS	— OCCASIONAL
CONTROLLABILITY	CONTROLLABLE	— UNCONTROLLABLE
FAMILIARITY	OLD	— NEW
BENEFIT	CLEAR	— UNCLEAR
NECESSITY	NECESSARY	— LUXURY

COMPARISON OF RCF VALUES

RCF	VALUE				
	LATAI & RASMUSSEN	ROWE	STARR	KINCHIN	OTWAY & COHEN
NATURAL/MAN-MADE	20	10			
ORDINARY/CATASTROPHIC	30	50			
VOLUNTARY/INVOLUNTARY	100	100	~ 1000		1 - 1000
DELAYED/IMMEDIATE	30	20%/YR		30	
CONTROLLABLE/UNCONTROLLABLE	5 - 10	100			
OLD/NEW	10				
NECESSARY/LUXURY	1				
REGULAR/OCCASIONAL	1				

UNCERTAINTY/ TOXICOLOGY

MANY ORDERS OF MAGNITUDE:

- BIOASSAY EXTRAPOLATION

- DOSE LEVEL DISTRIBUTION

- CURABLE CANCER

- SURROUNDINGS

- ANIMAL VARIABILITY

- INTERSPECIES COMPARISON

- COMPOUND PURITY

- GLPs

- SYNERGISM /ANTAGONISM

UNCERTAINTY/ TOXICOLOGY
(Con't)

LITTLE CHANGE UP TO
ONE ORDER OF MAGNITUDE:

- SELECTION OF DOSE LEVELS
- PRE-CURSERS
- DIET
- TIME-TO-TUMOR
- ADD BENIGN TUMORS
- DISEASE INTERFERENCE
- STATISTICAL NOISE
- NO CORRESPONDING HUMAN TUMOR
- BODY WEIGHT vs SURFACE
- UPPER 95% LIMIT
- HOUSEKEEPING

UNCERTAINTY/ TOXICOLOGY
(Con't)

ALL OR NOTHING:

- ENDPOINT

- DOSE LEVELS

- PERSONNEL

- SPECIES

- STRAIN

- AGE

- SEX

- STATISTICS

- HISTORY

- p LEVEL

Sources of Uncertainty for Occurrence, Population Concentration and Exposure Estimates Used in the Assessment of Volatile Organic Chemicals in Drinking Water

Factors	Impact on estimate of†:		
	Occurrence	Population Concentration	Risk

Generation of monitoring data

Proportion of population sampled	5% (U)		
Representativeness of systems selected			
Geographic distribution, system size and source of water	10% (E)		
Sampling methods		50%	Factor of two
Site of sample collection	20% (E)		
Time of sample collection	20% (E)		
Method of sample collection	10% (U)		
Container type	10% (U)		
Stability during storage	100% (U)		
Sample analysis			
% recovery from sample	10% (U)		
Compound identification	10% (E)		
Accuracy of quantitative determination	40% (E)		

Assumptions during data analysis

Lower limits of quantification		factor of 3-4	factor of 2 (E)
Oral exposure rates			
Intake rate of water			10% (E)
Pollutant level in concumed water(hot vs cold)			50% (O)
% absorption for oral intake			10% (O)
Respiratory exposure rates			Factor of 3
Dermal exposure			Negligible

†U = leads to an underestimation of the risk; O = leads to an overestimation of the risk; E = could lead to an overestimation or an underestimation of the risk.

Vinyl Chloride–Population Risk Estimates
For Current Levels of Drinking Water Exposure
(Maltoni–Old)

Mean Drinking Water Concentration (Micrograms/Liter)	Number of People Being Served	Total Lifetime Individual Risk For the Mean Concentration*		Population Risk
		Low (Probit)	High (Weibull)	
0.25	2.1×10^8	2×10^{-9}	2.1×10^{-4}	<1 - 50,000
2.75	1.3×10^6	3×10^{-7}	1.1×10^{-3}	<1 - 1430
7.5	4.7×10^5	1×10^{-6}	2.2×10^{-3}	<1 - 1030
65	1.2×10^5	9×10^{-6}	3.5×10^{-3}	<1 - 420

Total†   1 - 50,000

Vinyl Chloride(Maltoni)–Risk Reduction Analysis
For Limiting Drinking Water Concentration

Maximum Allowable Drinking Water Concentrations (Micrograms/Liter)	Approximate Individual Risk Rate for Maximum Concentration	Cumulative Cases Averted•
65	$6 \times 10^{-6} - 6 \times 10^{-3}$	<1 - 420
7.5	$3 \times 10^{-7} - 2 \times 10^{-3}$	<1 - 1450
2.75	$1 \times 10^{-7} - 1 \times 10^{-3}$	<1 - 2880

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† Rounded to one significant figure

* The total individual risk was determined by assuming that the risk due to inhalation is equal to that due to ingestion

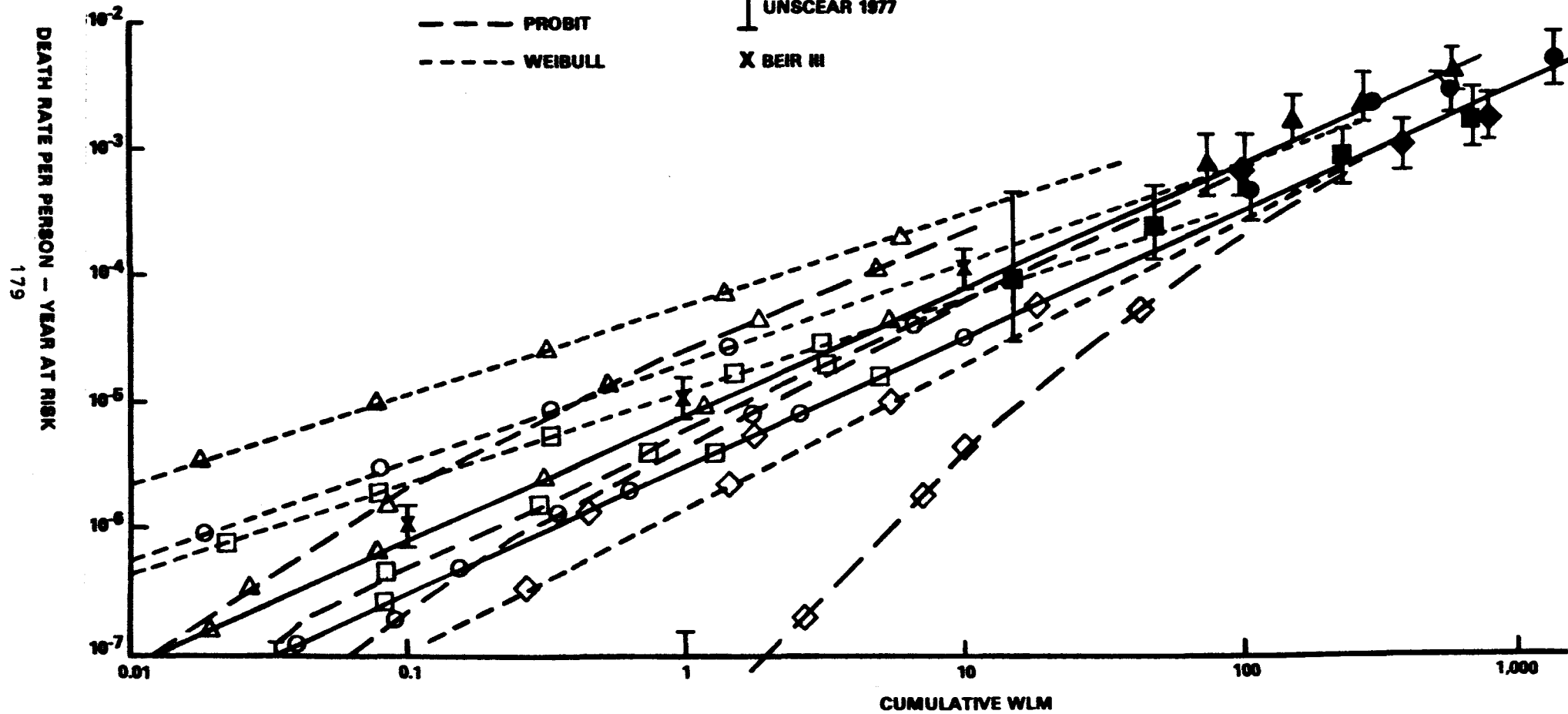• Number of cases averted for concentrations shown in first column

LEGEND

○ COLORADO PLATEAU URANIUM MINERS   □ SWEDISH METAL MINERS

△ CZECHOSLOVAKIAN URANIUM MINERS   ◇ NEWFOUNDLAND FLUOSPAR MINERS

SOLID MARKS ARE DATA — OPEN ONES IDENTIFY CURVES

———— MULTISTAGE

— — — PROBIT   ⊥ UNSCEAR 1977

- - - - WEIBULL   X BEIR III

DEATH RATE PER PERSON — YEAR AT RISK

CUMULATIVE WLM

ADVANTAGES AND UNCERTAINTIES OF ANIMAL DATA
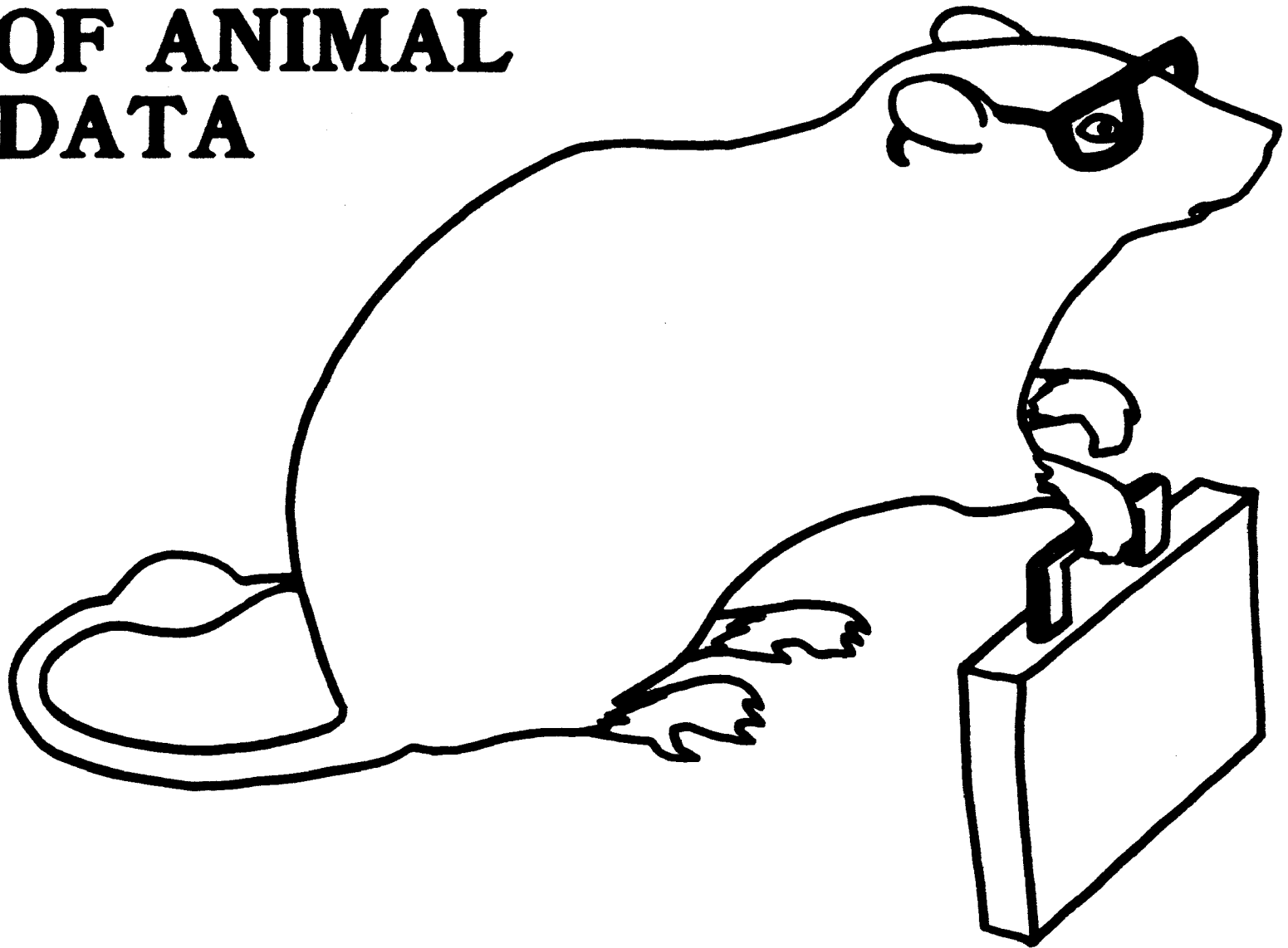
K.

CASE STUDY ON RISK ASSESSMENT OF
VINYL CHLORIDE

New information on the toxic properties of a widely used chemical, vinyl chloride (VC), has just been published in a major scientific journal. The uses of VC place it under the jurisdiction of EPA, and a senior agency policymaker must decide whether the new information justifies regulatory action. As a first step the policymaker must determine whether and to what extent current uses of VC endanger the public health. The senior policymaker thus assembled a group of top agency scientists from various disciplines -- epidemiology, toxicology, biochemistry, pathology, statistics, chemistry -- and posed the following questions:

1. What types of health hazards might be associated with VC, and how well are these known?

2. What is the magnitude of human exposure to VC, and how is the exposure distributed in various population groups?

3. What is the nature and magnitude of human risk associated with the various sources of exposure?

The group of scientists collected data to conduct a risk assessment. In particular, they developed information to estimate the likelihood that VC will exhibit one or more of its hazardous properties under actual conditions of human exposure. At this stage the senior policymaker is only concerned with understanding the risks of VC and the ways in which that risk can be characterized. The senior policymaker is not presently concerned with what has been referred to as risk management, or the issue of how to regulate VC if a risk has been identified. Hence, the senior policymaker is not considering the commercial importance of VC and the possible regulatory consequences of reporting a significant health risk.

The senior policymaker believes strongly that it would not be satisfactory to conclude that no risk assessment could be performed, or that "more research" had to be conducted before any conclusions could be reached. Rather, the senior policymaker felt it was essential that as definitive a statement as was currently possible be made about the health risk of VC, and that the uncertainties in the assessment be identified. The senior policymaker knew it would have to be decided how to handle the scientific uncertainties in the risk management decision, but for now the need was to understand and characterize the current scientific knowledge of the risks of VC.

YOUR ROLE

For this exercise, you will play the role of the senior policymaker.
Your objective is to ensure that you thoroughly understand the possible
health risks associated with various uses of VC and that you can convey
your understanding to other people. You are not yet concerned with the
ultimate regulatory question of whether and to what extent these uses
should be controlled or eliminated; you are concerned with the risk assess-
ment, not risk management.

You will receive various sets of data and analysis from the team of
scientists you have assigned to the problem. You will conduct an analysis
of the information and its implications for risk. You will review and
evaluate the contents of the document. You will be asked to formulate
some conclusions based on the data and analysis.

Your review and evaluation will take place within a small working
group. After the various issues are aired and discussed, the working
group (which collectively represents the senior policymaker) should reach
a consensus on how best to characterize the data and the risk. If a
consensus cannot be reached, the alternative views should be expressed.
The conclusions of each working group will then be compared and contrasted.

Again, at this stage you are concerned only with risk assessment,
not with risk management.

NATURE OF THE DATA AND ANALYSIS TO BE REVIEWED

The report contains a discussion of the nature and uses of VC, and
the known extent of human exposure to it. The toxicological data on VC
will be presented in summary form. You will be asked to examine several
issues relating to the data and reach conclusions regarding them. This
section constitutes the Hazard Evaluation.

The relationship between exposure to VC and the risk of adverse
health effects (Dose-Response Evaluation) is the next subject. There may
be several scientifically plausible options for describing this relationship
in the region of human exposure, and you will be asked to judge the
relative merits of these various options. That is, you will be asked to
choose among them, or formulate a better one.

The third section will contain a summary of data on the Exposure of
various population groups to VC. Again, several issues arise concerning
the interpretation and use of this information, and it will be necessary
for the senior policymaker to formulate appropriate conclusions.

In the final step (Risk Characterization) you will be asked to present
your conclusions regarding the human health risks posed by VC and the
uncertainties in your knowledge.

At each of the four major steps of this exercise, issues and data will be presented, and alternative conclusions will be listed. After discussion, you may select the conclusion that seems most appropriate; if none seems appropriate, you should offer your own.

RESOURCE MATERIAL

The document entitled Principles of Risk Assessment: A Non-Technical Review (Sec.II.I, pp. 79-130) provides background material needed to assist your evaluation. You also will be exposed to some key principles and additional background material at the two lectures to be presented before the group sessions.

In addition, each of the following sections contains a discussion of the key principles directly relevant to the specific issues under consideration.

I.   BACKGROUND INFORMATION ON VINYL CHLORIDE

USES OF VINYL CHLORIDE

° RAW MATERIALS   -   in plastics, rubber, paper, glass and automotive industries.

° MANUFACTURE OF   -   electric wire, insulation and cables, piping, industrial and household equipment, medical supplies, food packaging and building supplies.

CHEMICAL & PHYSICAL PROPERTIES OF VINYL CHLORIDE

° Structure   -

$$H-C=C-Cl$$
$$\quad | \quad |$$
$$\quad H \quad H$$

° Physical State   -   Gas

° Stability   -   Degrades rapidly in the environment

° Solubility in   -   1.1 g/L at 28°C
  Water

PRODUCTION IN U.S.A.   -   1983 -- 7 billion pounds

HUMAN EXPOSURE

° General Population -   Humans could be exposed to vinyl chloride in drinking water, food and air. Some people could be exposed also through occupational and consumer usage.

° Worker Populations -   Workers are exposed during manufacture.

II.   HAZARD EVALUATION

SOME PRINCIPLES FOR HAZARD EVALUATION

° The purpose of hazard evaluation is to identify the types of
  adverse health effects that may be associated with exposure to VC,
  and to characterize the quality and strength of evidence supporting
  this identification.

° The specific hazard of concern in this review is cancer.

° Epidemiological studies in exposed human populations generally are
  considered to be the best source of information for hazard identi-
  fication. Unfortunately, they are not available for most substances.
  Moreover, establishing firm causal links between exposure and
  human disease is very difficult.

° Studies in experimental animals also provide useful information
  for hazard identification. Such studies can be controlled, and
  thus can more easily establish causality. Results from such
  studies suffer from the obvious limitation that experimental
  animals are not the species of ultimate interest.

° With one possible exception (arsenic), all known human carcinogens
  also are carcinogenic in one or more experimental animal species.
  Many animal carcinogens have not been established as human
  carcinogens, in most cases because of the lack of adequate
  epidemiological data.

° There are biological reasons to believe that responses in
  experimental animals could be mimicked by responses in humans, a
  proposition supported by considerable empirical data. However,
  other data show that species differ in response to the same agent.

° It is known that the specific site(s) of tumor formation in humans
  may be different from that observed in experimental animals.

° Data obtained by administering a substance by the same route of
  exposure that is experienced by humans are considered more
  predictive than data obtained by a different route. But if tumors
  form at internal body sites, the route of exposure may not be
  important.

° In general, a varied response in experimental animals -- tumor
  formation in several species, both sexes, at several different
  exposure levels with increasing response at increasing exposure,
  and at multiple body sites -- provides more convincing evidence
  of potential human carcinogenicity than does a response that is
  limited to a single species or sex, or to a single common site of
  tumor formation.

A number of studies have been conducted in rats, mice and rabbits
which show that vinyl chloride is carcinogenic in these species. Statis-
tically significant increases in the numbers of tumors at a variety of
sites have been reported following both inhalation and oral exposure.

During the risk assessment case study, we are focusing upon the
results of just one of those studies. The reasons for this decision should
become clear as you become more acquainted with the data.

THE FERON, ET AL. STUDY

In 1981, an article by Feron, et al. entitled "Lifetime Oral Toxicity
Study of Vinyl Chloride in Rats" appeared in a respected scientific
journal (Food and Cosmetic Toxicology). This paper presented data on the
effects in rats of lifetime oral exposure to vinyl chloride. The design of
the experiments and the major findings are presented in Tables I and II.

TABLE I

Design of the Feron, et al. Study

Species & Route of Exposure	Grps.Receiving Vinyl Chloride	# of Animals		Amt VC Recd Each Day[1]	Duration of Exp. (weeks)
		Male	Female		
Rat, Dietary	Control	60	60	0	104
	Low Dose	60	60	1.7	104
	Mid Dose	60	60	5.0	104
	High Dose	60	60	14.1	104
Rat, Gavage	–	60	60	300.0	104

[1] The units of "amount received" are milligrams of vinyl chloride (VC)
per kilogram of the animal's body weight.

Note: Gavage is the administration of a substance by means of a stomach
tube.

TABLE II

Significant Findings from the Feron, et al. Study

Following are the groups in which a statistically significant excess of tumors was found. Complete assessment of tumor formation was made in each sex.

			Tumor Incidence (number of animals with tumors)			
Study Group	Sex	Tumors Found[a]	Control	Low-Dose	Mid-Dose	High-Dose
Rat, Dietary	Male	**Liver**				
		a. neoplastic nodule	0	1	7	24[c]
		b. hepatocellular carcinoma	0	1	2	9[c]
		c. angiosarcoma	0	0	6[c]	27[c]
		Lung				
		a. angiosarcoma	0	0	4[c]	19[c]
Rat, Dietary	Female	**Liver**				
		a. neoplastic nodule	2	26[c]	39[c]	44[c]
		b. hepatocellular carcinoma	0	4	19[c]	29[c]
		c. angiosarcoma	0	0	2	9[c]
		Lung				
		a. angiosarcoma	0	0	1	5[c]

			Dose[b]
Rat, Gavage	Male	**Liver**	
		a. neoplastic nodule	3
		b. hepatocellular carcinoma	1
		c. angiosarcoma	27
Rat, Gavage	Female	**Liver**	
		a. neoplastic nodule	2
		b. hepatocellular carcinoma	0
		c. angiosarcoma	29

[a] Tumors are described both in terms of target organ and tumor type within the target organ. There are three tumor types distinguished in liver.

[b] There was no matched control group with the treated group given VC by gavage. Thus, statistical comparison could not be done.

[c] A statistically significant excess of tumors relative to untreated control animals. This means that the difference in tumor incidence between the treated and control animals is not likely due to chance. Because the only difference between the control and treated animals was the presence of VC, it is thus likely that the excess tumor incidence is due to this compound. Tumors were found at other sites in both control and treated animals, but no others occurred in statistically significant excess.

REMARKS ON THE FERON, ET AL. STUDY

1. As far as can be determined from the published Feron, et al. article, this study was carefully conducted and there is no reason to doubt the accuracy of the reported data.

2. VC increased the <u>incidence of risk of tumors</u> (number of animals with tumors) in all groups of animals given VC in the diet, although the increase in low-dose males was not statistically significant.

3. Rats treated with VC by gavage developed the same tumor types in liver as those treated with VC in the diet, but lung angiosarcomas were not apparent with gavage exposure.

4. Rats developed liver tumors following both dietary and gavage exposures. Lung tumors were produced only by dietary exposure.

5. Following dietary exposure to VC, females showed more neoplastic nodules and hepatocellular carcinomas, whereas males showed more angiosarcomas in liver and lung.

6. Neoplastic nodules and hepatocellular carcinomas were proportionally greater than liver angiosarcomas with dietary exposure to VC, whereas the opposite was evident with gavage exposure to VC.

7. Liver and lung tumors observed in treated animals are rarely formed in untreated (control) rats of the strain (Wistar) used by Feron, et al. This is particularly important in the interpretation of liver tumor data in rats treated with VC by gavage as a treatment-related effect.

8. Neoplastic nodules are considered to be a progression towards hepato-cellular carcinomas and are, therefore, included in the tumor incidence table. These tumor types are of different cellular origin, and are thus considered distinct tumor types from liver angiosarcomas.

9. Identification of tumor types in each animal individually was not given. Therefore, for the purpose of quantitative risk assessment, animals with hepatocellular carcinoma also are assumed to have neoplastic nodules. Therefore, only neoplastic nodules and angio-sarcomas are added together to derive total liver tumors.

ISSUES TO BE CONSIDERED BY THE SENIOR POLICYMAKER

1. How do these data conform (or not conform) to the principles laid out on page II-1 -- particularly the last one?

2. In view of these principles, is there any reason to conclude that VC is not carcinogenic in rats of both sexes (by dietary and gavage exposures)?

3. Is there any reason to believe that humans would not be at risk of developing these various tumors, assuming they were exposed to VC?

4. Is there any way to determine, from the data given, whether responses in humans are likely to be similar to those of rats? Males or females?

5. Should the liver tumors be considered relevant to humans?

6. Should the data obtained by gavage treatment be considered relevant to human exposure?

CONCLUSIONS REGARDING VC CARCINOGENICITY

Which of the following conclusions best characterize the evidence you have seen?

1. VC is a human carcinogen.

2. VC is a probable human carcinogen.

3. VC is a carcinogen at several sites in rats of both sexes, by both dietary and oral routes of administration. VC is thus a human carcinogen and is expected to increase the incidence of lung and liver tumors in the exposed human population.

4. VC is a carcinogen at several sites in rats of both sexes. VC is thus a probable human carcinogen, although only humans exposed orally are likely to be at risk. Data obtained when VC was administered by stomach tube are not relevant to any route of human exposure. Thus, exposure through other routes has no identifiable risk for humans.

5. Although VC is carcinogenic in rats, no data suggest that it is carcinogenic in humans. The animal data provide only weak evidence that VC may be a human carcinogen.

6. Because of the extreme conditions under which tumors were produced in these animal experiments, there is no reason to believe VC is a possible human carcinogen.

7. Other (formulate your own conclusion).

III.   DOSE-RESPONSE EVALUATION

THE GENERAL PROBLEM AND PRINCIPLES GUIDING APPROACHES TO ITS SOLUTION

Because of the relative complexity of dose-response evaluation, the following discussion is substituted for a statement of key principles.

Recall that animal data showing that a chemical is carcinogenic usually are obtained in the high exposure region of the dose-response curve. Thus, animal exposures were in the 1.7 to 300 mg/kg/day ranges (Table I). Human exposure is in the range of 0.03 to 2.0 ug/kg/day over a range of potential drinking water concentration levels (Table VI). What can be said about risks in the range of human exposure?

At least three general approaches to this problem have been proposed by various experts.

Approach 1

Based on general theories of how carcinogens act to produce cancer (largely derived from experimental studies and epidemiological data), all finite exposure levels will produce a finite risk. The magnitude of the risk will decline as the magnitude of exposure declines (this is even clear in the animal data).[1]

If the quantitative relationship between exposure and risk were known for all exposures, risk to rodents exposed at very low levels could be predicted from the measured exposure-risk data. Risks to humans could be predicted at these very low levels if the relationship between rodent and human susceptibilities were known. Although these relationships cannot be known with accuracy, a plausible upper limit on human risk can be predicted with sufficient accuracy to be used as a guide to making risk decisions. Actual human risk is not likely to exceed the upper limit (although it may), and it may be less.

Approach 2

The quantitative relationships between high exposure and low exposure risks in rodents and between rodent and human risk are not known with sufficient reliability to be used in risk assessment. Moreover, there is no reliable theory on which it can be concluded with assurance that low-level human exposure (i.e., exposure below the range producing detectable risks) poses any risk at all. As with other toxic effects, carcinogenicity will not be initiated within an individual until a minimum threshold of

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[1] These two sentences are the proper formulation of the "no-threshold" concept. The "no-threshold" concept does not mean that all finite exposures will cause cancer; instead, it means that all finite exposures will increase the probability that cancer will occur.

exposure is exceeded. In such circumstances, the only reasonable course is to report the magnitude of the margin of safety (MOS) by which humans are protected. MOS is the maximum amount of exposure producing no measurable tumorigenic response in animals divided by the actual amount of human exposure. MOS gives the risk manager adequate information on which to decide whether exposures must be reduced or eliminated to provide human protection. A relatively large MOS is desirable because it is likely that the threshold for the entire human population is substantially lower than that observed in small groups of experimental animals.

Approach 3

Although there is adequate theory and some evidence to permit the conclusion that humans are at finite risk at all finite exposure levels, there is insufficient knowledge to allow prediction of the risk in quantitative terms. The risk assessor should simply attempt to describe risks qualitatively, perhaps coupling this description with some information on the potency of the compound and the magnitude of human exposure. This type of presentation is adequate for the risk manager, who should not be concerned with the quantitative magnitude of risk in any case.

*　*　*　*　*

Each of these views, and perhaps others as well, has some merit. It would seem that the first approach, if correct, would provide the most useful approach for decision making. Indeed, it is the approach now used by EPA and other agencies as well. EPA and the other agencies emphasize that the predicted numerical risks are not known to be accurate, but, because of the nature of the models used to predict them, they are likely to be upper bound estimates of human risk. An upper bound estimate is one that is not likely to be lower than the true risk.

For this exercise we shall estimate low exposure risks using the model currently used by EPA. A model is a mathematical formula that describes the relationships between various measures. Two models are needed to predict low exposure risk:

○ A high-to-low exposure extrapolation model is needed to predict low exposure risks to rodents from the measured high exposure-high risk data (Table II). EPA currently uses a so-called linearized multistage model for this purpose. This model is based on general (not chemical-specific), widely held theories of the biological processes underlying carcinogenesis. Application of the model to the rodent exposure risk data produces an estimate of the lifetime risk for each unit of exposure in the low exposure region. This is called the unit cancer risk. The "linearized" model is used to ensure that the unit cancer risk is an upper bound on risk.

192

° An <u>interspecies extrapolation model</u> is used to extrapolate from rodent unit risks to human unit risks. There are empirical data and theory to support EPA's current use of the assumption that rodents and humans are at equal risk at the same exposure measured in milligrams of carcinogen per square meter of body surface area per day.

EPA's selection of these models is based on the agency's view that they are the best supported for purposes of deriving an upper bound estimate of risk. Alternative models are available for both these forms of extrapolation and cannot be ruled out. In most cases, but not always, use of plausible alternative models will yield lower estimates of risk than those predicted by the two described here. Differences can sometimes be very large, but in most cases differences are relatively small, especially when the models are limited to those which are linear at low exposure.

Further discussions of various models and their plausibility can be found in the resource material.

APPROACH TAKEN FOR THIS EXERCISE

In this exercise we reveal the upper bound of unit cancer risks predicted for VC using the models currently preferred by EPA. The effect of using alternative, plausible models is also described.

Estimates of Upper Bound, Lifetime Unit Cancer Risks Using Current EPA Models

Application of the EPA models for high-to-low dose and interspecies extrapolation to the measured animal cancer data of Table II yields the results shown in Table III.

Estimates of Lifetime Unit Cancer Risks Using Other Models

Application of <u>other models for high-to-low dose extrapolation</u> usually yields unit risks equal to or slightly lower than those in Table III, as long as the other models incorporate the concept that risk increases in direct proportion to exposure in the low exposure region (linear models).

Adoption of certain nonlinear models for high-to-low dose extrapolation predicts risk about 1,000 to 10,000 times lower than those predicted by use of the EPA model. The nonlinear models are not widely recommended.

TABLE III

Upper Bounds on Lifetime Unit Cancer Risks Predicted from
Application of EPA's Preferred Model to Tumor Data, Table II

Species, Sex	Route of Exposure	Tumor Site	Unit Cancer Risk[1]
Rat, Male	Diet	Lung	0.11
Rat, Male	Diet	Liver	0.3
Rat, Male	Diet	All tumors	0.29
Rat, Female	Diet	Lung	0.058
Rat, Female	Diet	Liver	1.9
Rat, Female	Diet	All tumors	2.3

[1]Risk for an average daily lifetime exposure of 1 unit
Units are same as those used earlier for describing the
animal exposure (Table I) and the human exposure (Table V)
(mg/kg bw/day). Risk is obtained from unit risk by multiply-
ing the latter by the actual number of units of human
exposure;the higher the unit risk, the higher the risk.

Dose-Response Evaluation not Involving Formal Extrapolation

For those who believe formal extrapolation beyond the measurable
dose-response data should not be performed, it is important to identify
the exposures at which VC produces tumors and those at which no tumor
excess is found (the "no observed effect level" or NOEL). Table IV
identifies NOELs from data in Table II.

TABLE IV

No-Observed Effect Levels (NOELs)
for Chronic Exposure to VC

Study Group	Sex	Tumor	NOEL[1]
Rat, dietary	Male	Liver	1.7
Rat, dietary	Female	Liver	None found
Rat, dietary	Male	Lung	1.7
Rat, dietary	Female	Lung	5.0
Rat, gavage	Male	Liver	None found
Rat, gavage	Female	Liver	None found

[1] Units are expressed as mg/kg bw/day. "None found" means
that a measurable excess of tumors was found at all
levels of exposure used in the experiment.

ISSUES TO BE CONSIDERED BY THE SENIOR POLICYMAKER

1. Which of the three possible approaches should be taken? Explicit
    estimate of risk? Quantitative estimate of MOS? Qualitative
    descriptions only? Should other approaches be considered?

2. If explicit estimates of unit risks are made, should only EPA's
    currently preferred models be used? Should the results of applying
    other models also be displayed?

3. Which species/sex/tumor site data from Table III should be used for
    unit risk assessment? All, shown individually as in Table III? Only
    the data set yielding the highest unit risk? A sum of all? Other?

4. How should the uncertainties in use of models be described?

5. Are the observed NOELs true "no-effect" levels? Could they simply
    reflect the fact that in experiments with relatively small numbers
    of animals, the failure to observe a statistically significant
    increase of tumors is an artifact of the experimental design, and
    not a true absence of biological effect? How should this uncertainty,
    if it is real, be taken into account?

ALTERNATIVE CONCLUSIONS REGARDING DOSE-RESPONSE EVALUATION

1. The unit cancer risks listed in Table III are true upper
   bound estimates. The true unit risk is not likely to
   exceed those determined, may be lower, and could be zero.

2. The same as the first conclusion, but add: The use of
   alternative, plausible models yields unit risks about 10 to
   100 times lower than those from Table III.

3. Unit risks should be reported for all plausible models, and
   the full range of estimates should be reported without bias.

4. There is no justification for calculating and reporting unit
   risks. What is critical for understanding the public health
   importance of low level exposure to VC is the margin of safety
   (MOS). Estimation of the MOS is based on the NOELs for its
   carcinogenic effects; these figures are reported in Table IV.

5. Neither unit cancer risks nor NOELs are reliable indicators of
   human risk, and neither should be considered for risk assess-
   ment. Dose-response relations for the human population are
   not known for VC; risk should be described in qualitative
   terms only.

6. Other (formulate your own conclusion).

IV.   HUMAN EXPOSURE EVALUATION

SOME PRINCIPLES FOR EXPOSURE EVALUATION

   ° The purpose of the exposure evaluation is to identify the magnitude
     of human exposure to VC, the frequency and duration of that exposure
     and the routes by which humans are exposed. The number of exposed
     people also must be identified, along with other characteristics
     of the exposed population (e.g. age and sex).

   ° Exposure may be based upon measurement of the amount of VC in
     various media (air, water, food) and knowledge of the amount of
     human intake of these media per unit of time (usually per day)
     under different conditions of activity.

   ° Some individuals may be exposed by contact with several media.
     It is important to consider total intake from all media in
     such situations.

   ° Because only a limited number of samples of various media can be
     taken for measurement, the representativeness of measured values
     of environmental contaminants are always uncertain. If a sampling
     is planned adequately, the degree to which data for a given medium
     are representative of that medium usually can be known.

   ° Sometimes air levels of pollutants can be estimated by the use of
     mathematical models. Although some of these models are known to
     be predictive in many cases, they are not thought to be so in
     other cases.

   ° Standard average values and ranges for human intake of various
     media are available and generally are used unless data for
     specific agents indicate such values are inappropriate.

AVAILABLE INFORMATION ON VINYL CHLORIDE

       The following information has been summarized from the Human
Exposure section of the Office of Drinking Water Criteria Document on
Vinyl Chloride. Use this information in formulating your risk assessment
decision.

       Humans may be exposed to vinyl chloride in drinking water, air and food.
This analysis is confined to these three media since they are considered
to be general sources common to all individuals. Some individuals may be
exposed to VC from sources other than those cited here, notably in
occupational settings and from the use of consumer products containing
vinyl chloride.

       Unfortunately, data and methods to estimate exposure of identificable
population subgroups from all sources simultaneously have not yet been developed.
To the extent possible, estimates are provided of the number of individuals
exposed to each medium at various VC concentrations. The 70 kg adult
male is used for estimating intake.

Water

Cumulative estimates of the U.S. populations exposed to various VC levels in drinking water from public drinking water systems are presented in Table V. Of the approximately 1.3 million people exposed to levels ranging from 1 to 5 ug/L, 0.9 million (65%) obtain water from surface supplies. All exposure to VC in drinking water at levels above 5 ug/L is expected to be from groundwater sources.

No data were obtained on regional variations in the concentration of VC in drinking water. The highest concentrations are expected to be near sites of polyvinyl chloride production.

Table V also shows daily intake levels of VC in drinking water estimated at various exposure levels. The data in the table suggest that the majority of the persons using public water supplies would be exposed to intake levels below 0.028 ug/kg bw/day.

Table V

Estimated Drinking Water Intake of Vinyl Chloride

Exposure level (ug/L)	Persons using supplies exposed at indicated levels		Intake (ug/kg/day)
	Population	% of total population	
$\geq$ 1	1,922, 000	0.9%	$\geq$ 0.028
> 5	591,000	0.3%	> 0.14
> 10	118,000	0.1%	> 0.29
> 50	118,000	0.1%	> 1.4
> 70	0	0	> 2.0

Assumptions: 70 kg adult male, 2 liters of water per day

Diet

No data were obtained on levels of VC found in foods in the United States. Therefore, no estimates of the daily intake of VC from the U.S. diet could be made.

Air

Exposure to vinyl chloride in the atmosphere varies from one location to another. The highest level of VC reported in the atmosphere was 2100 ug/m^3. High levels (> 15 ug/m^3) have been detected in other areas. Normal levels, however, are somewhat lower. Brodzinsky and Singh (1982) calculated a median air level of 0.0 ng/m^3 (0.0 ug/m^3) in each of three types of areas: rural/remote, urban/suburban and source-dominated.

The monitoring data are not sufficient to determine regional variations in the exposure levels.

Table VI describes the daily respiratory intake of VC from air as estimated using the assumptions presented and ther maximum and minimum ambient levels reported above. Intake calculated using the maximum VC level reported is 690 ug/kg/day; few, in any, persons are believed to be exposed to that level. Estimated daily intake under other circumstances is estimated to be 0 ug/kg/day.

Table VI

Estimated Respiratory Intake of Vinyl Chloride

Exposure (ug/m^3)	Intake (ug/kg/day)
Rural/remote (0.0)	0
Urban/suburban (0.0)	0
Source dominated (0.0)	0
Maximum (2100)	690

Assumptions: 70 kg adult male; 23 m^3 of air inhaled/day (ICRP, 1975)

ISSUES TO BE CONSIDERED BY THE POLICYMAKER

° Is there any reason to believe that animal data obtained from
continuous lifetime exposure should not be used to characterize the
risk to people exposed intermittently?

CONCLUSIONS REGARDING HUMAN EXPOSURE TO VINYL CHLORIDE

1. Although the estimates for air and water are based upon different
data and different assumptions, these data are adequate for
assessing vinyl chloride risks. The risk manager should be made
aware of the uncertainties in each of the data sets.

2. In addition to Conclusion #1, it should be noted that all the
exposures should be added because some people will be exposed to
all sources of vinyl chloride.

3. None of the exposure estimates is adequate for use in risk
assessment. The risk assessment should describe exposure in
qualitative terms only. Such a qualitative description is
appropriate and adequate for characterizing risk, which also can
be done in qualititative terms only.

4. Other (formulate your own conclusion).

V.   RISK CHARACTERIZATION

<u>PURPOSE</u>

In the last step of risk assessment, the information collected and analyzed in the first three steps is integrated to characterize the risks to humans. In line with the alternative approaches for describing dose-response relations, at least three approaches can be taken to this step.

1. Provide an explicit numerical estimate of risk for each population group by multiplying the unit risk <u>times</u> the number of units of exposure experienced by each group:

    (unit cancer risk) x (units of exposure) = risk

    In this equation, risk is unitless -- it is a probability.

Equation:

Unit risk x Ingestion volume x Body weight x Conversion of mg to ug x Unit(s) of exposure

2. Provide an estimate of the MOS for each group by dividing the NOEL by the exposure experienced by that group.

3. Describe risks qualitatively for each of the population groups.

Risk characterization also might include some combination of all three approaches, along with a description of their relative merits.

It also is essential that the statistical and biological uncertainties in estimating the extent of health effects be described in this step.

Attached you will find Appendix 1: Unit Risk Assessment for Vinyl Chloride. This document describes the use of Feron, et al. data for the estimation of a unit risk for oral exposure to vinyl chloride.

In Table VII, the risks for each population group using data from Table V are reported. These risks are based on the <u>highest</u> unit cancer risk described in the Appendix (a_1* = 2.3 $(mg/kg/day)^{-1}$ for all tumors combined. If other unit risk figures from Table III had been used, somewhat lower risks would result. And, if unit cancer risks derived from other dose-response models had been used, the risks shown may be 10 to 100 times lower. The risks in Table VII are thought to be upper bound lifetime risks.

TABLE VII

Risks in Each Population Group for Risk Characterization

Source	Risk	Size of Population Group	Upper Bound on Number of Cancer Cases over Lifetime
Drinking Water alone at:			
0 ug/L	0	220 million +	0
1 ug/L	7×10^{-5}	1.9 million +	133
5 ug/L	3×10^{-4}	591,000	177
10 ug/L	7×10^{-4}	118,000	83
50 ug/L	3×10^{-3}	118,000	354
70 ug/L	5×10^{-3}	0	0

ISSUES TO BE CONSIDERED BY THE SENIOR POLICYMAKER

1. Are the results reported in Table VII an adequate characterization of VC risks? What else should be added?

2. Should risks derived from all the unit risks reported in the Appendix and unit risks obtained using alternative models also be reported?

3. The risks and number of cases reported in Table VII depend on the assumption that the number of people exposed and their level of exposure will remain constant over a lifetime. Is this a plausible assumption? Can alternative assumptions be used?

4. Is it important to distinguish routes of exposure? Should unit risks obtained from the inhalation data be used only for population groups exposed by inhalation? Should gavage data be used at all?

5. Is it important to know whether a finite risk exists at all exposure levels, or whether a threshold exists?

6. Is it appropriate to estimate the number of cancer cases expected by multiplying risk times population size (last column of Table VII)? What is more important -- risk to an individual, or risk to a population?

7. What are the biological and statistical uncertainties in estimating the number of expected cancer cases? How should they be estimated and described?

ALTERNATIVE CONCLUSIONS

1. Upper bound risks to humans exposed to VC are those reported in Table VII. Although risks obtained from the use of other models may be lower, the risks could be as high as those reported in Table VII.

2. The risks shown in Table VII, as well as those obtained from use of all other plausible models and all of the various tumor site data, should be reported, and all estimates should be given equal weight. Such a presentation affords the decision maker a view of the uncertainty in the estimated risks.

3. Upper bound estimates of lifetime risks to humans are those reported in Table VII. Use of all other animal data sets and alternative, plausible risk models would result in prediction of lower risks, perhaps up to 100 times lower. These risks are conditional on the assumption the VC is a probable human carcinogen, based solely on observations of carcinogenicity in several species of experimental animals. Uncertainties in exposure and population estimates are those described in the Exposure Assessment section.

4. VC is a probable human carcinogen, based on observations of carcinogenicity in more than one animal species. Exposures needed to produce animal carcinogenicity are many thousands of times higher than those to which humans are exposed. The margins of safety by which humans are protected are shown in Table VII. Because a NOEL has not been identified for all the various carcinogenic endpoints, a greater than usual MOS should be employed to protect human beings.

5. VC is a probable human carcinogen, based on observations of carcinogenicity in more than one species of animals. Humans may be exposed through air, water and during employment. In general, small numbers of people may be exposed continuously to very low levels of VC, and a few groups are exposed inter-mittently. The individual risk in the general population is probably low to moderate, but this translates to a relatively large number of cancer cases because of the large population size, etc.

6. Other? Some combination of the others?

APPENDIX 1

UNIT RISK ASSESSMENT FOR VINYL CHLORIDE

The data used to estimate a unit risk for oral exposure to vinyl chloride are based on the Feron et al. (1981) study. The statistically significant increases reported for liver and lung tumors were considered biologically significant. For the liver tumors, neoplastic nodules were considered a progression toward hepatocellular carcinomas, and these are included in the analysis in Tables 1 and 2. Extrapolations using the linearized multistage model show values of q_1^* for the individual tumors ranging from 8.8×10^{-2} to 1.3×10^{-1} for the males and from 5.8×10^{-2} to 1.3 for the females. The value of q_1^* based on males was 3.0×10^{-1} for liver tumors and 2.9×10^{-1} based on all tumors combined. For the females the value of q_1^* based on liver tumors was 1.9 and for all tumors combined was 2.3. All units of q_1^* are per mg/kg/day.

Before proceeding with the unit risk estimates an explanation of the total tumor counts in Tables 1 and 2 is necessary. For the liver all animals with hepatocellular carcinomas were assumed to also have the neoplastic nodules. Thus, only the neoplastic nodules and liver angiosarcomas were added to derive the total liver tumors. Otherwise, the totals would have exceeded the number of animals examined. Also, in adding the lung and liver tumors, the totals were not allowed to exceed one less than the number examined. The

Table 1 Type and Incidence of Statistically Significant Treatment-Releated
Changes in the Liver and Lung of Male Wistar Rats Exposed to VCM in
the Diet. Values of q_1^* and Concentration from Multistage
Extrapolation Model Included

	Treatment group (mg/kg/day)				q_1^{*a} (mg/kg/day)$^{-1}$	95% lower-limit concentration associated with risk (ug/L)^b		
	0	1.7	5.0	14.1		10^{-4}	10^{-5}	10^{-6}
Number of rats examined^c	55	58	56	59				
Liver								
Neoplastic nodules	0	1	7	23	2.1×10^{-1}	16.7	1.7	0.2
Hepatocellular carcinomas	0	1	2	8	8.8×10^{-2}	39.8	4.0	0.4
Angiosarcomas	0	0	6	27	1.3×10^{-1}	27.0	2.7	0.3
Total liver tumors^d	0	2	13	50	3.0×10^{-1}	11.7	1.2	0.1
Lung								
Angiosarcomas	0	0	4	19	1.1×10^{-1}	31.8	3.2	0.3
Total animal with tumors^e	0	2	17	58	2.9×10^{-1}	12.1	1.2	0.1

^{a}Human equivalent $q_1^* = q_1^*$ (a) $(W_h/W_a)^{1/3}$ in (mg/kg/day)$^{-1}$.
^{b}Concentration in ug/L $= (-35,000/q_1^*)$ ln(1-R).
^{c}Found dead or killed in extremis or terminally.
^{d}Sum of neoplastic nodules and liver angiosarcomas.
^{e}Total must be at least less than total examined.

Table 2 Type and Incidence of Statistically Significant Treatment-Related Changes
in the Liver and Lung of Female Wistar Rats Exposed to VCM in the Diet. Values
of q_1^* and Concentration from Multistage Extrapolation Model Included

	Treatment group (mg/kg/day)				q_1^{*a} (mg/kg/day)$^{-1}$	95% lower-limit concentration associated with risk (ug/L)[b]		
	0	1.7	5.0	14.1		10^{-4}	10^{-5}	10^{-6}
Number of rats examined[c]	57	58	59	57				
Liver								
Neoplastic nodules	2	26	39	44	1.3	2.7	0.3	0.03
Hepatocellular carcinomas	0	4	19	29	5.0×10^{-1}	70.0	0.7	0.07
Angiosarcomas	0	0	2	9	8.8×10^{-2}	39.8	4.0	0.4
Total liver tumors[d]	2	26	41	53	1.9	1.8	0.2	0.02
Lung								
Angiosarcomas	0	0	1	5	5.8×10^{-2}	60.3	6.0	0.6
Total animal with tumors[e]	2	26	42	56	2.3	1.5	0.2	0.02

[a]Human equivalent $q_1^* = q_1^*$ (a) $(W_a/W_e)^{1/3}$ in (mg/kg/day)$^{-1}$.
[b]Concentration in µg/L $= (-35,000/q_1^a)\ln(1-R)$.
[c]Found dead or killed in extremis or terminally.
[d]Sum of neoplastic nodules and liver angiosarcomas.
[e]Total must be at least less than total examined.

result of this latter restriction was to raise the value of q_1^* slightly due to increased variance. In fitting the response data in Tables 1 and 2 with the human equivalent dosages, the human equivalent dosages were derived by dividing the corresponding animal dosages by $(W_h/W_a)^{1/3}$. The human weight (W_h) was assumed to be 70 kg; the male rats were estimated to weight 350 g and the female rats were estimated to weigh 200 g (Figure 1). Thus, the corresponding human equivalent dosages were 0, 0.29, 0.85, and 2.41 mg/kg/day based on the male rats, and 0, 0.24, 0.71 and 2 mg/kg/day based on the female rats.

When the response and human equivalent dose data were fit to the linearized multistage model, the 95% upper limit on the largest linear term (Table 2) was:

$$q_1^* = 2.3 \text{ (mg/kg/day)}^{-1}$$

To derive an estimate of the 95% lower level of concentration, d, corresponding to a 95% upper level of risk, R, the following equation is used:

$$R = 1 - e^{-q_1^* d}$$

where d is the lower limit on dose in mg/kg/day. To solve for d in ug/L, we use the transformation

$$1 \text{ mg/kg/day} \times (70 \text{ kg/2 L}) \times 1,000 \text{ ug/mg} = 35,000 \text{ ug/L}$$

Duration of experiment, wk

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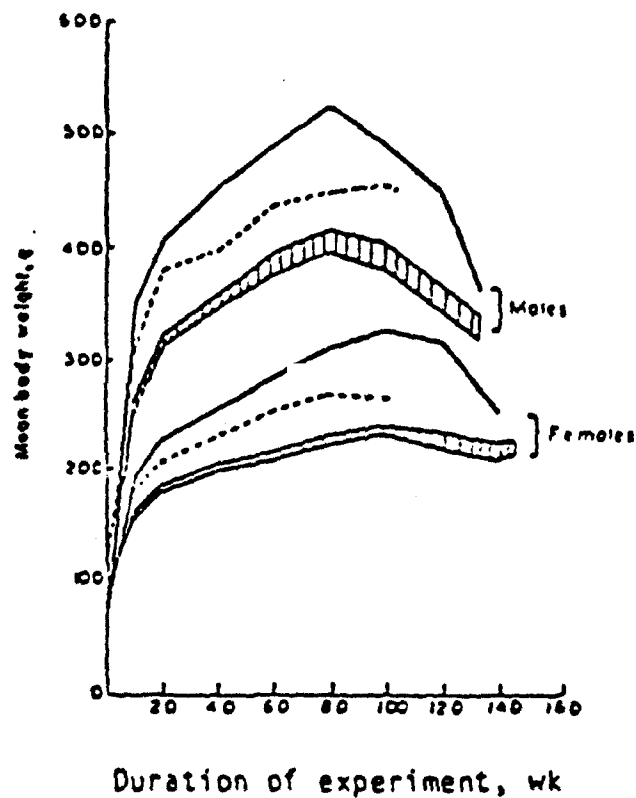
[a] *The weight curves of the rats receiving 0, 1.7, 5.0 or 14.1 mg VCM/kg body weight/day from the 10% PVC diets fed for four hours each day all lie within the shaded area.*

Adapted from Feron et al. 1981.

Figure 1   Average Body Weights of the Extra Controls Fed the 10%-PVC Diet Ad Libitum (-) and of the Rats Given 300 mg VCM/kg Body Weight in Oil by Gavage[a]

If we set $R = 10^{-5}$ then

$$d = (-35,000/q_1^*) \ \ln \ (1-10^{-5}) \ (ug/L).$$

For the highest value of $q_1^* = 2.3 \ (mg/kg/day)^{-1}$ (Table 2), setting $R = 10^{-5}$ yields a value of $d = 0.15$ ug/L. Setting $R = 10^{-4}$ or 10^{-6} yields values of $d = 1.5$ ug/L and $d = 0.015$ ug/L, respectively.

For comparison purposes only we compare the potency of vinyl chloride by the diet versus the inhalation routes. A previous memo we sent you estimated the 95% upper limit of potency for VCM as $q_1^* = 1.7 \times 10^{-2} \ (mg/kg/day)^{-1}$ based on an inhalation study showing angiosarcomas and other tumors in rats. That potency estimate was derived for water quality criterion purposes. In that document an inhalation to ingestion by gavage relationship of 1 ppm inhaled = 2.28 mg/kg/day ingested was derived for 200 g rats based on VCM uptake study. Without that adjustment for route differences, a direct transformation based on a 70 kg human breathing 20 m^3/day would have yielded a 1 ppm inhaled = 0.76 mg/kg/day relationship and a $q_1^* = 5.2 \times 10^{-2}$ mg/kg/day, still 44 times less than the estimate from the diet study.

In summary, the VCM potency estimates are reported in Table 3.

Table 3 VCM Potency Estimates

Route	Potency $q_1^*(mg/kg/day)^{-1}$	95% lower limit concentration associated with risk (ug/L)		
		10^{-4}	10^{-5}	10^{-6}
Oral				
Based on diet study	2.3	1.5	0.15	0.015
Based on inhalation study	1.7×10^{-2}	200	20.0	2.0
Inhalation				
Based on inhalation study	5.2×10^{-2}	67.3	6.7	0.7

PART III

REGULATIONS AND ASSESSMENT OF RADIONUCLIDES IN DRINKING WATER
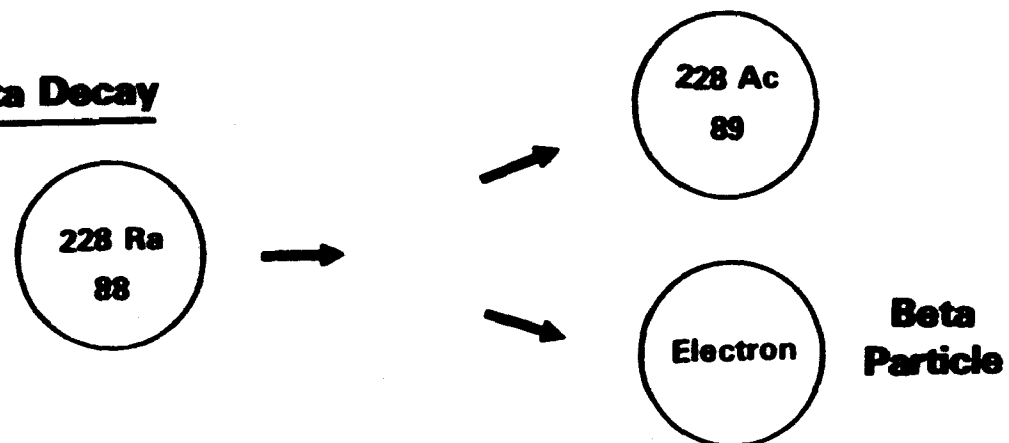
Phase III

Radionuclides

Alpha Decay

$$^{222}_{86}Rn \longrightarrow \begin{cases} ^{218}_{84}Po \\ ^{4}_{2}He \end{cases}$$

Alpha
Particle

Beta Decay

$$^{228}_{88}Ra \longrightarrow \begin{cases} ^{228}_{89}Ac \\ Electron \end{cases}$$
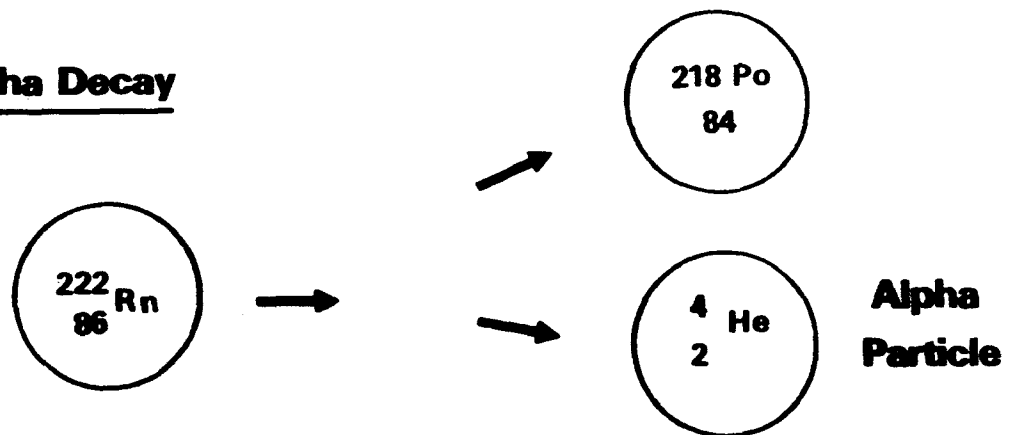
Beta
Particle

CONSIDER 238_U AND $228R_a$

BOTH ARE RADIOACTIVE AND GO TO THE BONE

BUT---THEY ARE DIFFERENT

HALF LIVES 4.5×10^9 yr vs 6.7 yr

PARTICLE EMITTED Alpha vs Beta

NEED UNITS TC DESCRIBE

NUMBER OF PARTICLES/SEC----ACTIVITY

1 CURIE = NUMBER OF PARTICLES/SEC FROM

ONE GRAM OF RADIUM

TYPE AND ENERGY OF PARTICLE---DOSE

1 RAD IS 100 ERGS/GRAM OF ENERGY DEPOSITED

(REM IS DOSE EQUIVALENT SINCE Alpha IS MORE

EFFECTIVE THAN Beta)
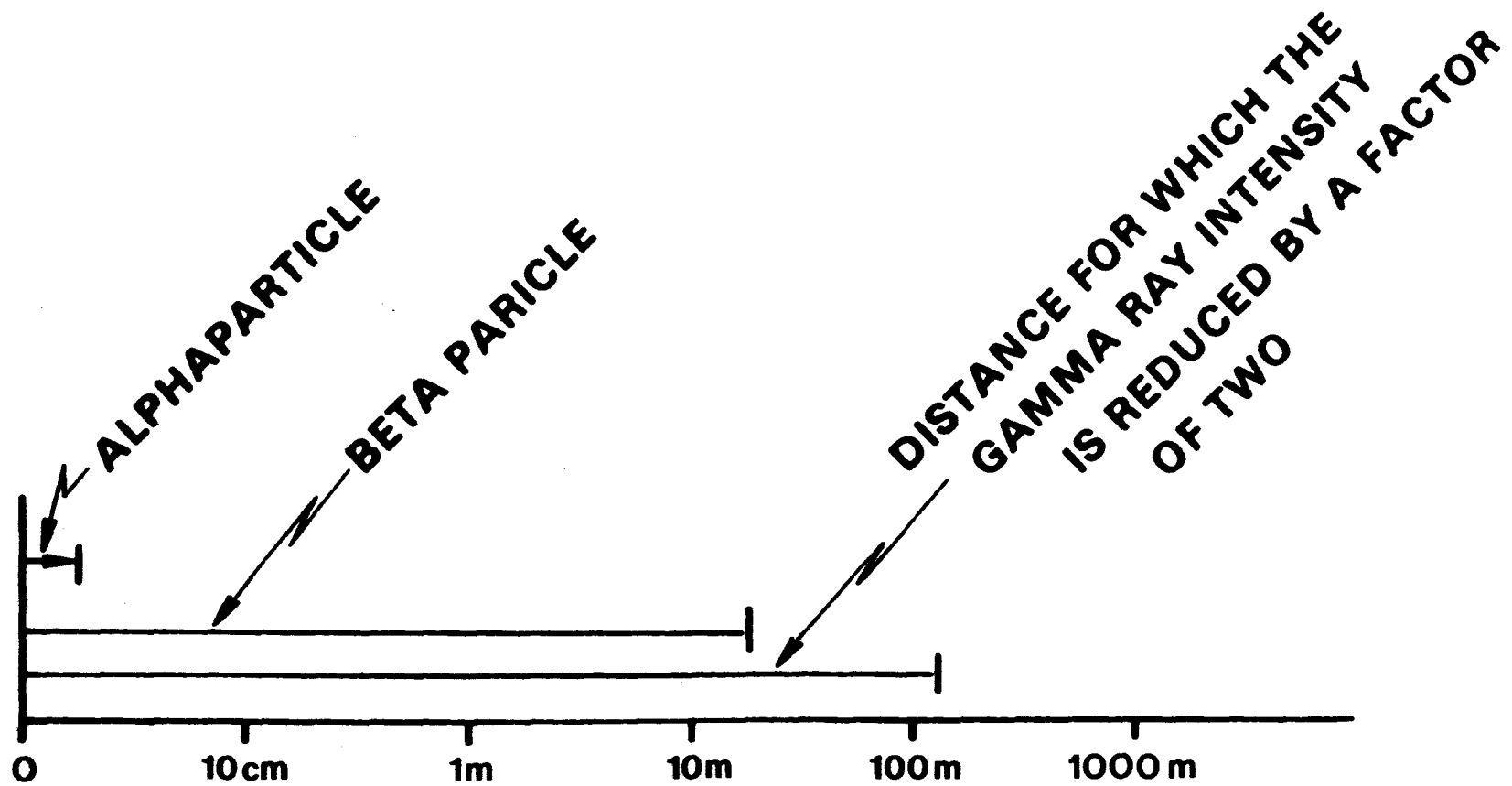
GREEK PREFIX	ABBREVIATION	VALUE	ENGINEERING SHORTHAND	
mega	M	1,000,000	10^{6}	
kilo	k	1,000	10^{3}	
milli	m	$\dfrac{1}{1000}$	10^{-3}	ONE PART PER THOUSAND
micro	μ	$\dfrac{1}{1,000,000}$	10^{-6}	ONE PART PER MILLION(ppm)
nano	n	$\dfrac{1}{1,000,000,000}$	10^{-9}	ONE PART PER BILLION(ppb)
pico	p	1/1,000,000,000,000	10^{-12}	
femto	f	1/1,000,000,000,000,000	10^{-15}	

THE URANIUM SERIES
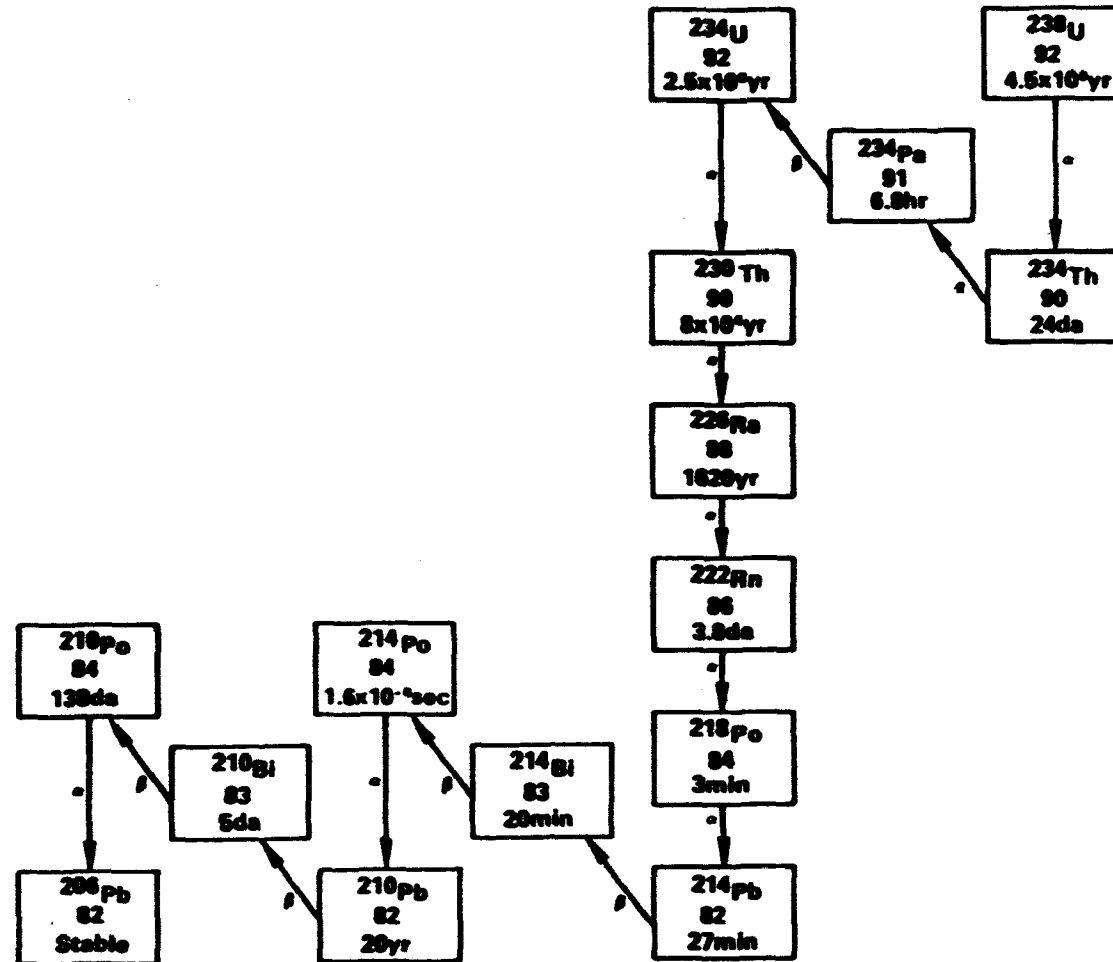
THE THORIUM SERIES

218
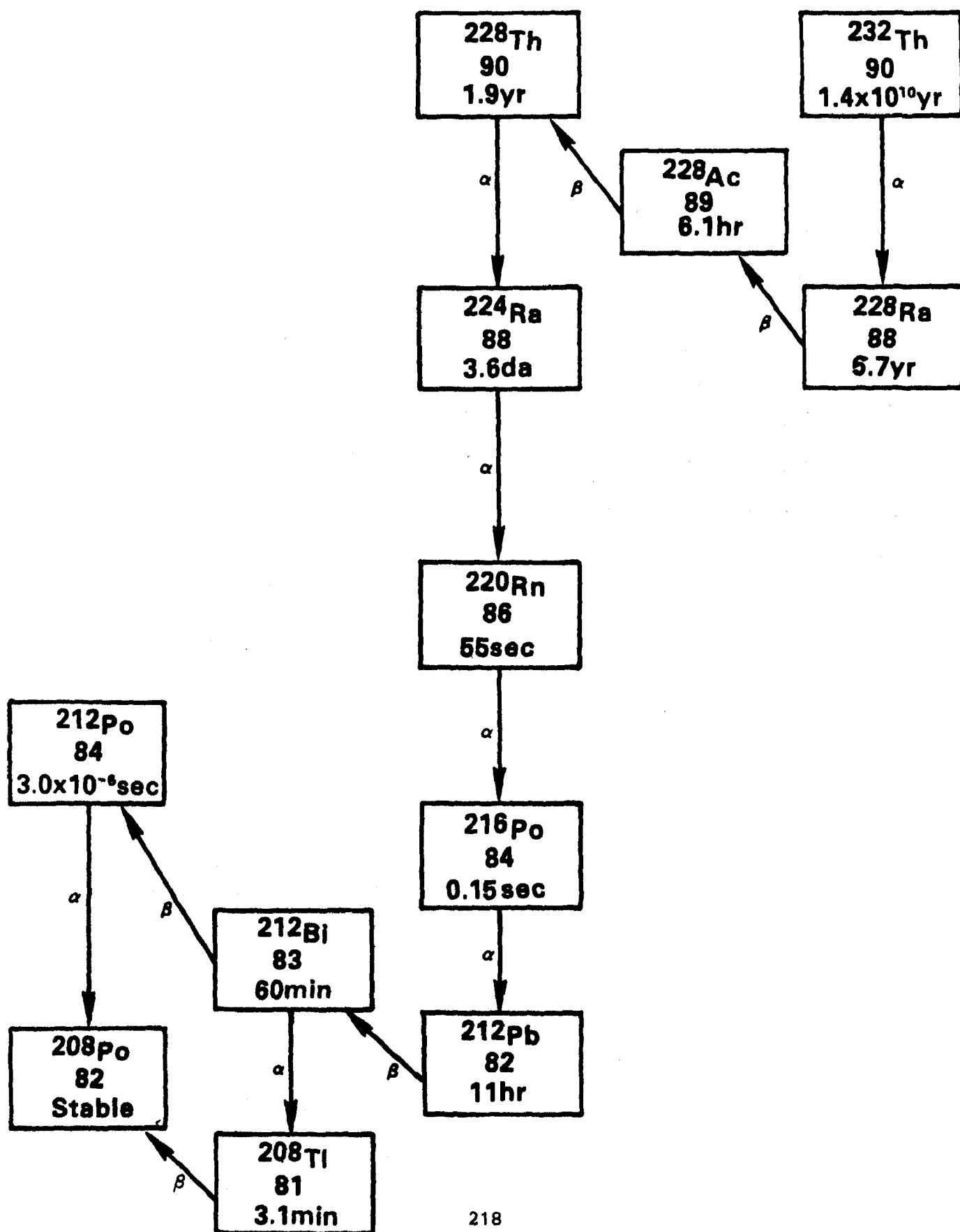
AVERAGE ANNUAL EFFECTIVE DOSE EQUIVALENT TO HUMANS FROM NATURAL BACKGROUND

| Organ	Weighting factor	Annual dose equivalent (mSv/y)	Annual effective dose equivalent (mSv/y)
Gonads	0.25	0.97	0.24
Breast	0.15	0.95	0.14
Lung			
Mean Dose	0.12	0.96	-
Trachial/Bronchial	0.06	14.0	-
Pulmonary	0.06	1.8	-
Total	-	-	1.0
Red Bone Marrow	0.12	1.1	0.13
Bone Surfaces	0.03	1.9	0.057
Thyroid	0.03	0.88	0.026
Other	0.30	0.97	0.29

Total = 1.9 mSv/y

(or approximately 200 mrem/y)

RADIONUCLIDES: DEFINITIONS

- **Types of nuclear radiation:** alpha, beta and gamma

- **Activity** - rate at which nuclear radiations are emitted
  - Curie (Ci) - one gram of radium-226; equal to 3.7×10^{10} disintegrations per second
  - Becquerel (Bq) - one disintegration per second

- **Dose Equivalent:** effect of ionizing radiation on tissue
  - Rem: unit of dose equivalent from ionizing radiation to total body or any internal organ or organ system
  - Sievert: one sievert equals 100 rem

- **Working Level (WL):** used to describe dose due to progeny of radon

- **Organ Weighting Factors**
  - relative sensitivities of organs to ionizing radiation
  - yields effective dose equivalent that can be summed for all organs

INTERIM REGULATIONS FOR RADIONUCLIDES IN DRINKING WATER

- Gross Alpha Particle Activity - 15 pCi/l (excludes uranium and radon)

- Combined 226_{Ra} and 228_{Ra} - 5 pCi/l

- Gross Beta Particle Activity - 50 pCi/l (for surface water supplies that have population exceeding 100,000)

- Man-Made Radionuclides - 4 mrem/yr (approximately 200 radionuclides)
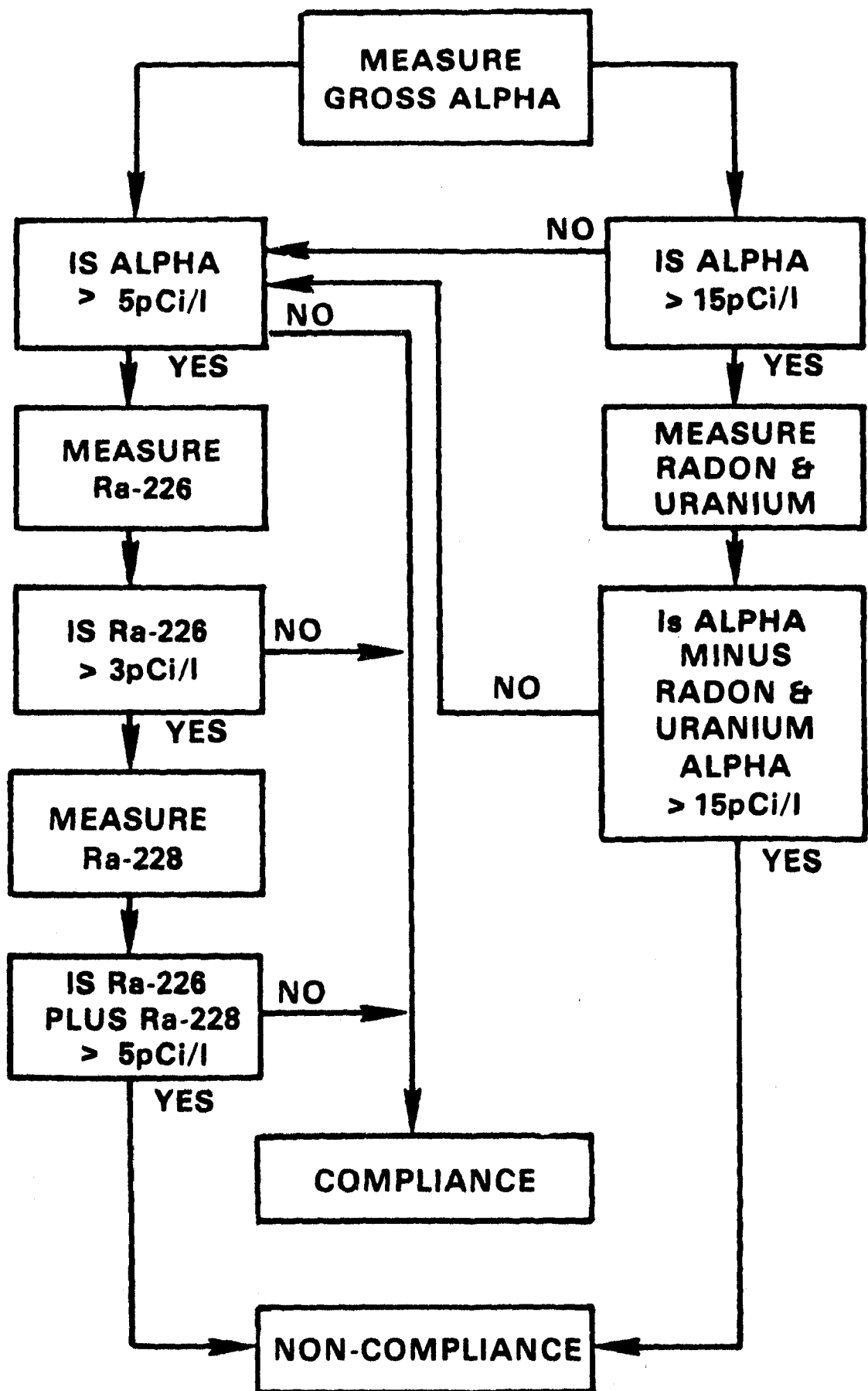
STRENGTH OF EVIDENCE OF CARCINOGENICITY: RADIONUCLIDES

Radionuclide	EPA Guidelines Category
radium-226	A
radium-228	A
natural uranium	A*
radon	A
gross alpha	A
gross beta and photon emitters	A

*by inference

PROPOSED MCLGs FOR RADIONUCLIDES

Radionuclide	MCLG
Radium-226	zero
Radium-228	zero
Radon	zero
Uranium-natural	zero
Gross Alpha Emitters	zero
Gross-Beta and Photon Emitters	zero

RADIUM OCCURRENCE

compliance data
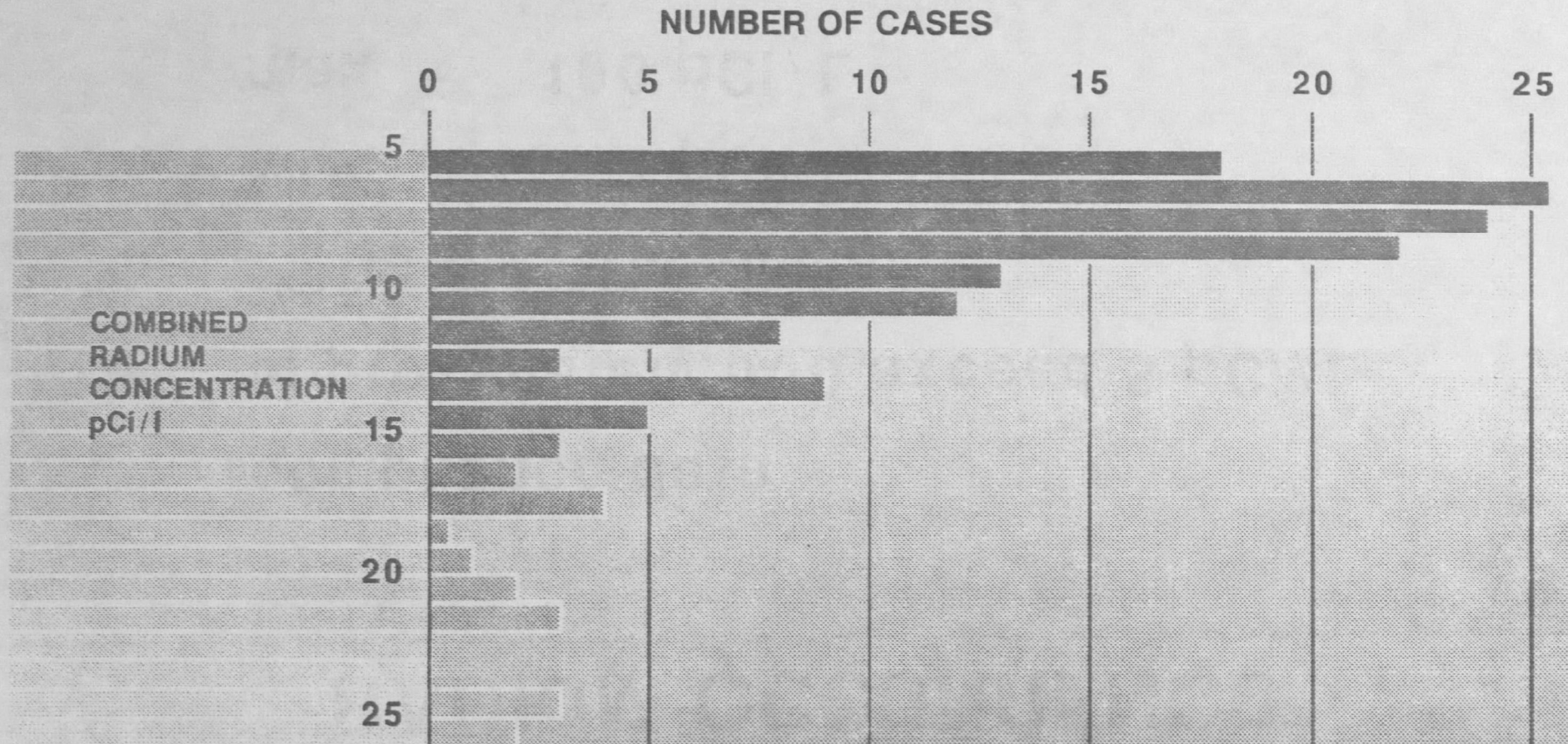
approximately 500 exceed 5 pCi / L

^{226}Ra & ^{228}Ra similar

MDL   1 pCi / L

max   100 pCi / L

DISTRIBUTION OF COMBINED RADIUM IN DRINKING WATER

NUMBER OF CASES

226

DISTRIBUTION OF GROSS ALPHA PARTICLE ACTIVITY IN DRINKING WATER
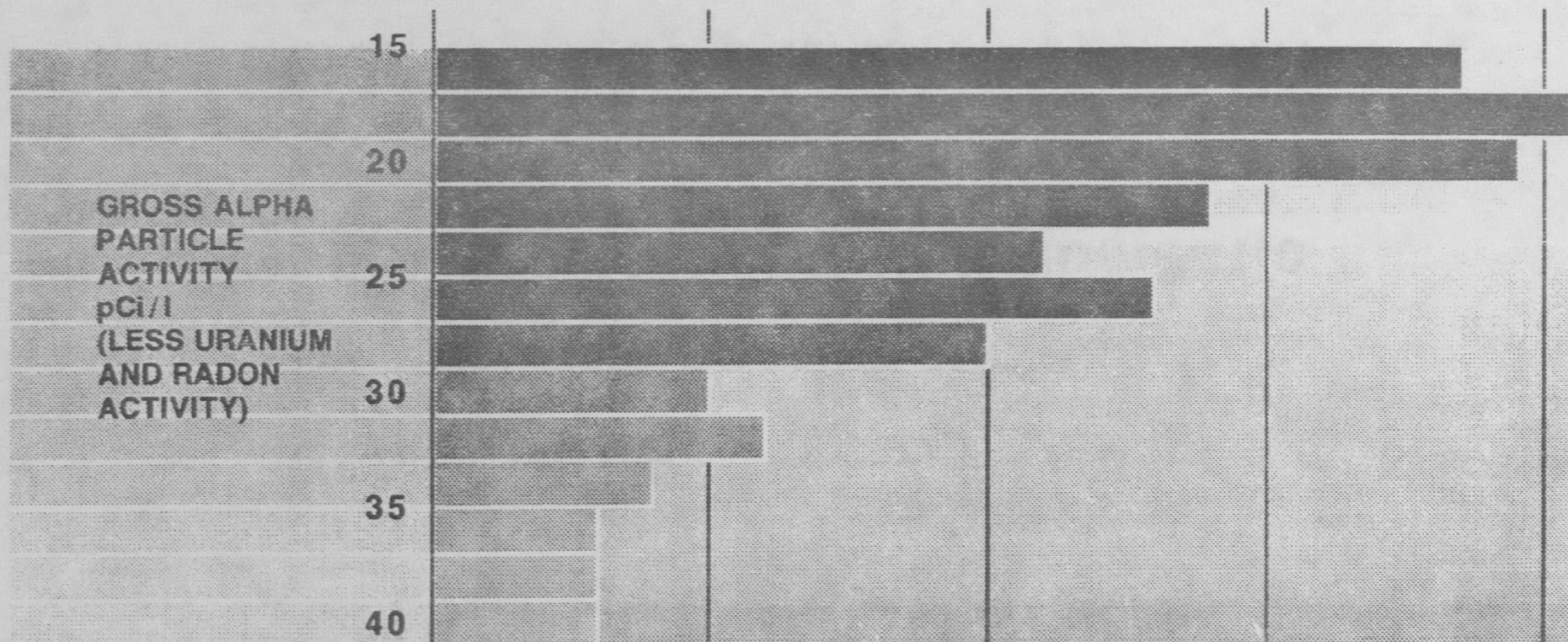
Number of Cases

GROSS ALPHA PARTICLE ACTIVITY pCi/l (LESS URANIUM AND RADON ACTIVITY)

227

URANIUM OCCURRENCE

USGS / NURE

89,000 ground and surface

approximately 20,000 domestic

MDL   **1 pCi / L**

max   **600 pCi / L**

average   **2 pCi / L**

^{234}U / ^{238}U

DISTRIBUTION OF URANIUM OCCURRENCE IN DRINKING WATER

NUMBER OF SAMPLES

229
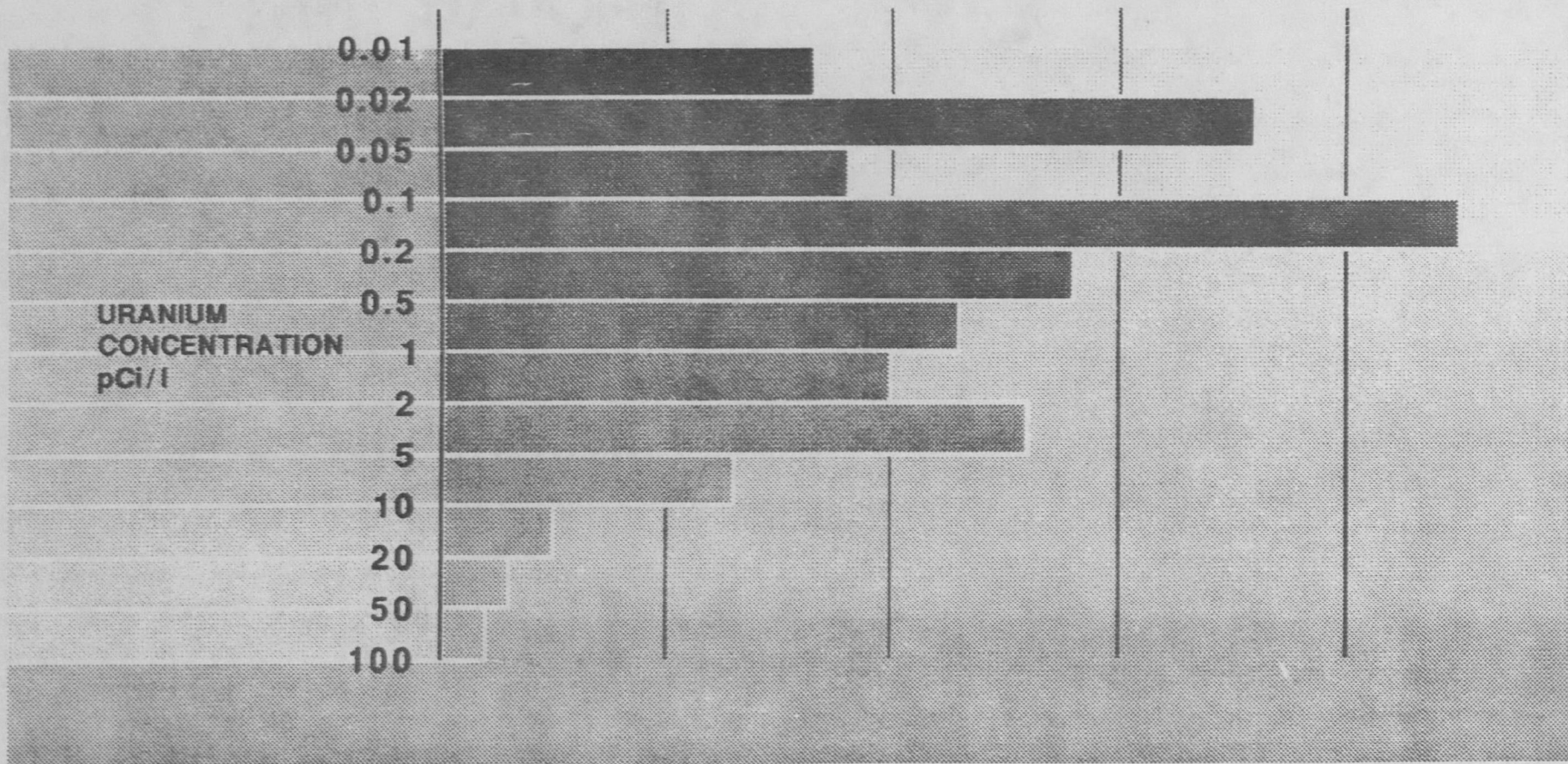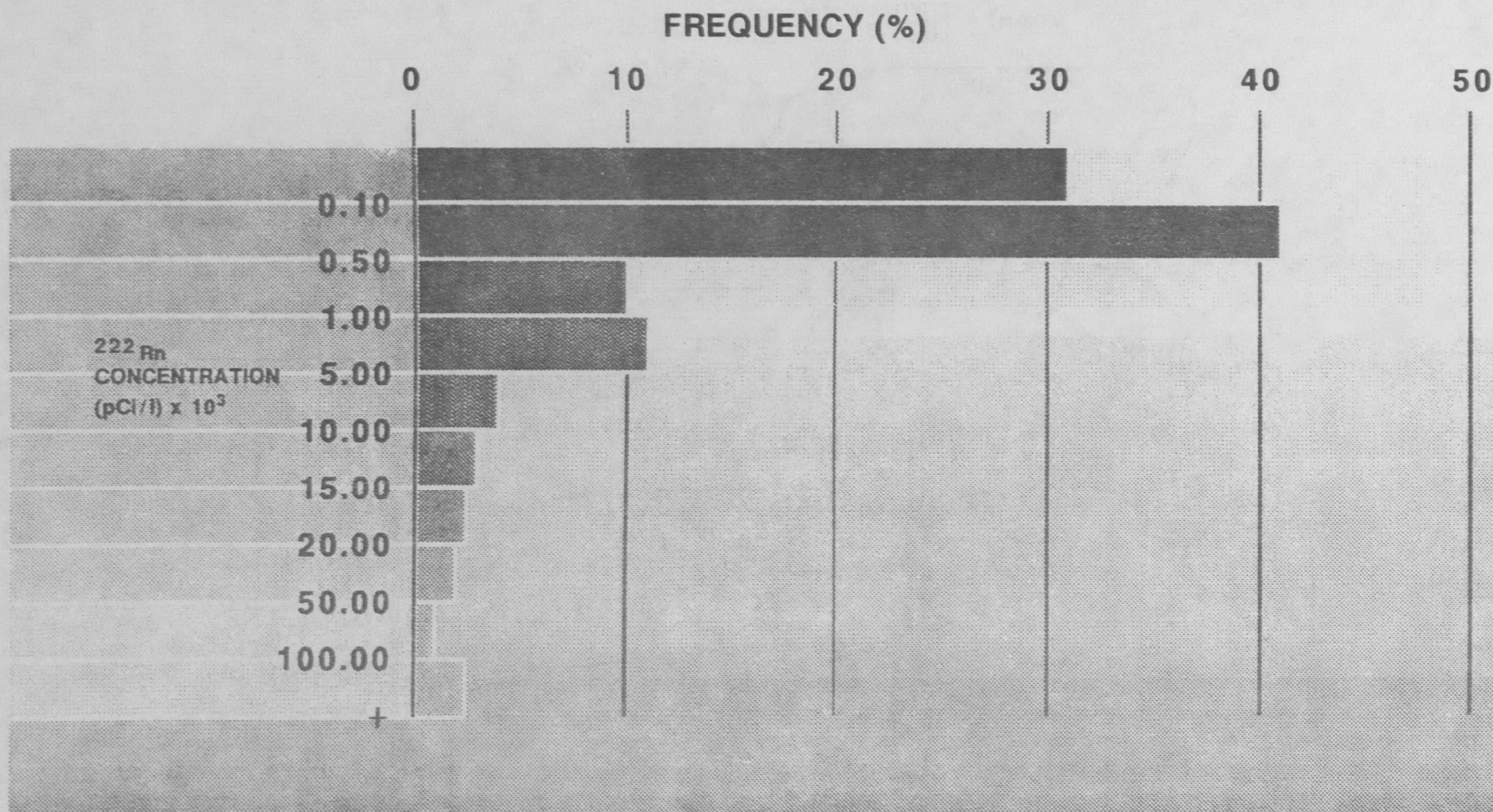
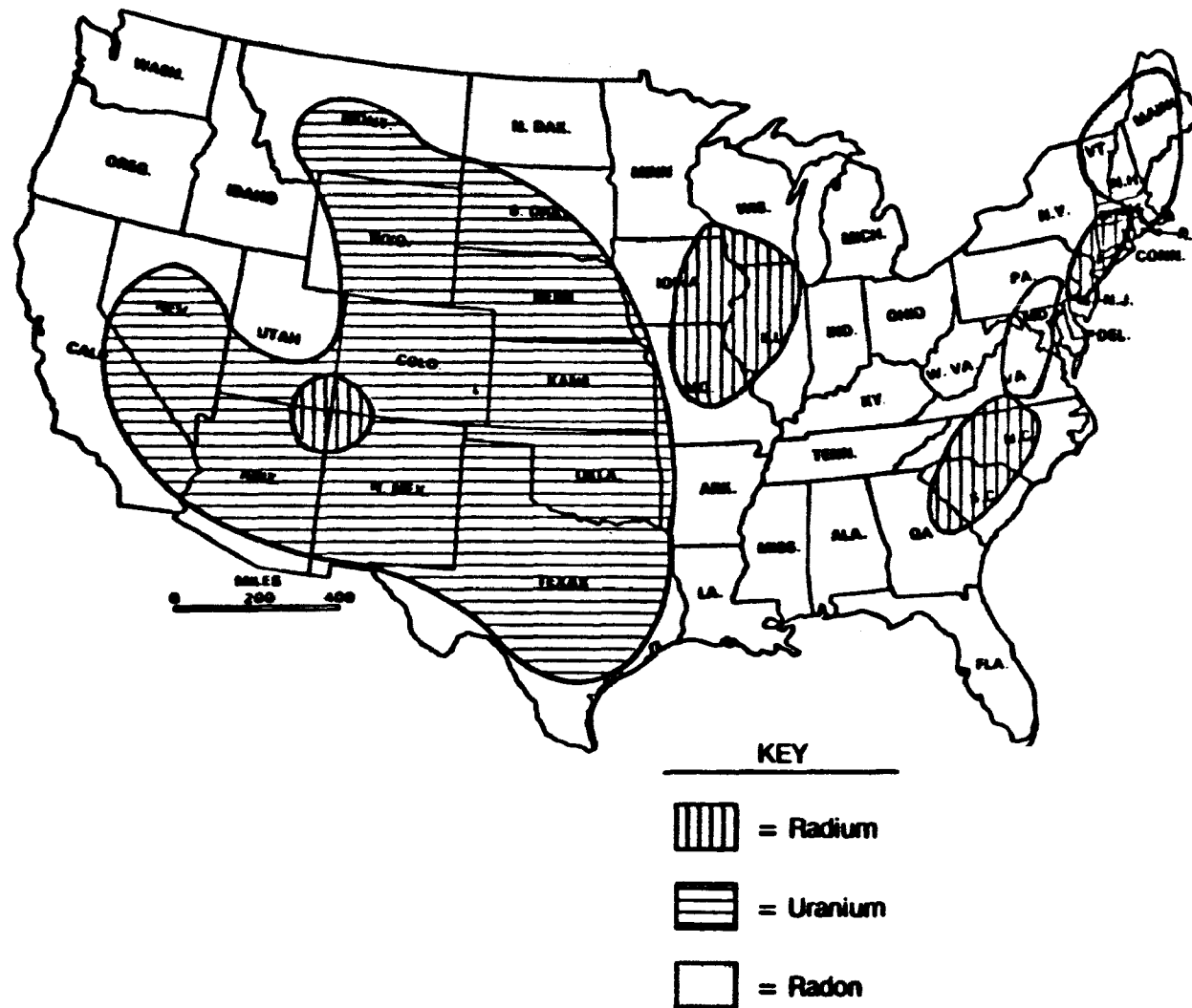# RADON OCCURRENCE

- EERF survey

- workshop report

- private wells - factor of 3 to 4 higher

- ground water

- MDL 10 pCi / L

- max 2,000,000 pCi / L

DISTRIBUTION OF RADON
IN DRINKING WATER

FREQUENCY (%)

AREAS OF NATURAL RADIOACTIVITY IN DRINKING WATER

KEY

|||| = Radium

≡ = Uranium

☐ = Radon

DISTRIBUTION OF AREAS OF RELATIVE RISK OF HAVING ELEVATED Ra-228 IN COMMUNITY GROUND WATER SUPPLIES

■ HIGH   □ MEDIUM   □ LOW
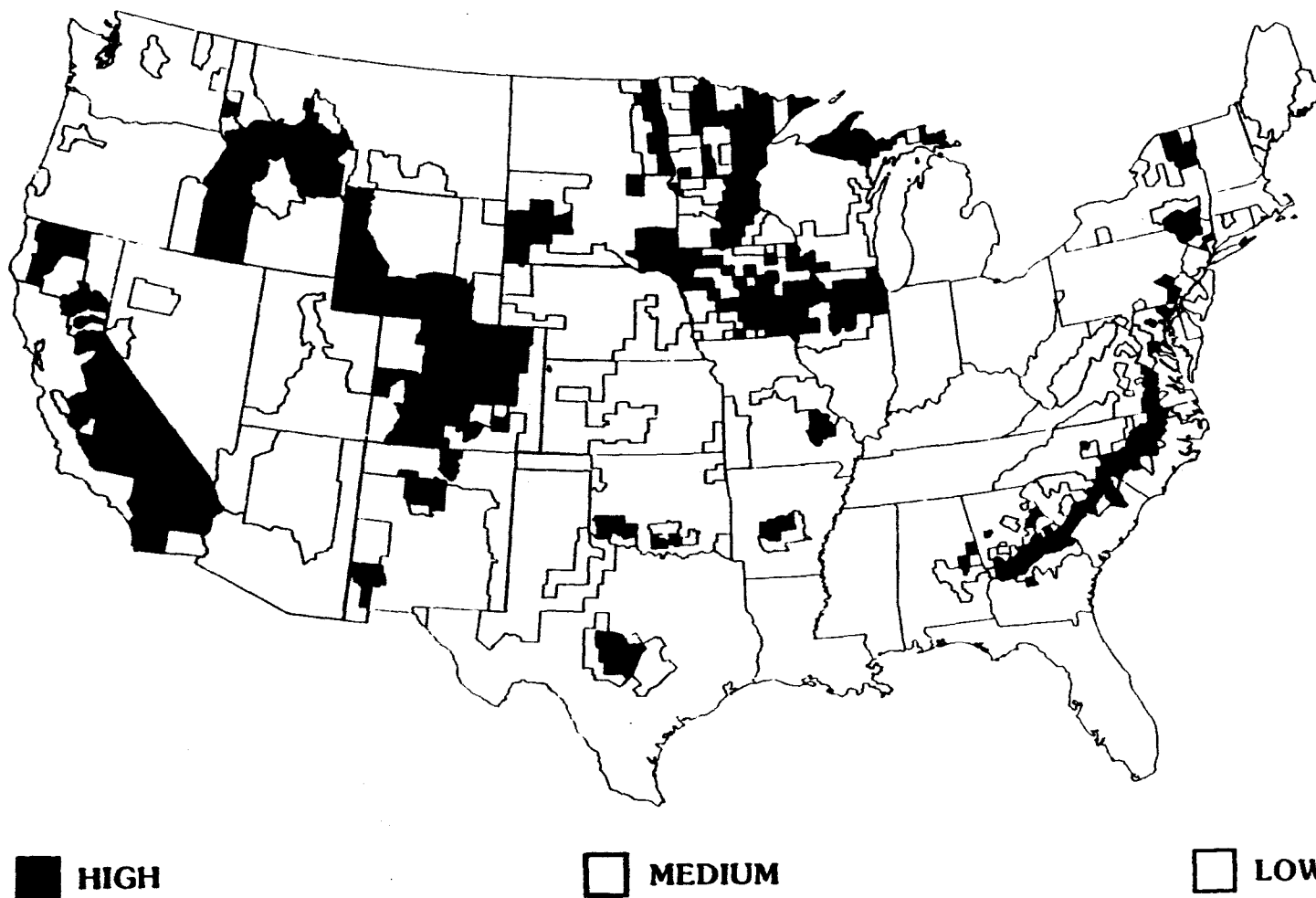
POPULATION WEIGHTED AVERAGE

$$\frac{\left(\text{Concentration}\right) \times \left(\begin{array}{c}\text{number of people exposed}\\ \text{to that concentration}\end{array}\right)}{\text{total number of people}}$$

234

OCCURRENCE OF NATURAL RADIONUCLIDES
IN DRINKING WATER SUPPLIES

Radionuclide	Average population-weighted concentrations (average of surface and ground water supplies) (pCi/l)
Radium-226	0.3-0.8
Radium-228	0.4-1.0
Uranium-natural	0.3-2.0
Radon-222	50-300
Lead-210	<0.11
Polonium-210	<0.13
Thorium-230	<0.04
Thorium-232	<0.01

AVERAGE RELATIVE SOURCE CONTRIBUTION
TO THE DAILY INTAKE OF NATURAL RADIONUCLIDES

Radionuclide	Source	pCi / d
^{226}Ra	air	0.007
	food	1.1 - 1.7
	drinking water	0.6 - 2
^{228}Ra	air	0.007
	food	1.1
	drinking water	0.8 - 2
$^{234}U + ^{238}U$	air	0.0007
	food	0.37 - 0.9
	drinking water	0.6 - 4
^{210}Pb	air	0.3
	food	1.2 - 3.0
	drinking water	< 0.22

AVERAGE RELATIVE SOURCE CONTRIBUTION TO THE DAILY INTAKE OF NATURAL RADIONUCLIDES (Continued)

Radionuclide	Source	pCi/d
^{210}Po	air	0.06
	food	1.2-3.0
	drinking water	<0.26
^{230}Th	air	0.0007
	food	probably negligible
	drinking water	<0.08
^{232}Th	air	0.0007
	food	negligible
	drinking water	<0.02
^{222}Rn	outdoors (1.8 Bq/m^3)	970
	indoors (15 Bq/m^3)(g)	8,100
	drinking water	100-600

GENERAL RADON INFORMATION

indoor 1 pCi / L (air)

outdoor 0.1 pCi / L (air)
[or about 1,000 pCi / L (water)]

national average in water
200 to 600 pCi / L

10^{-4} risk level - few hundred pCi / L

RADIUM HEALTH EFFECTS

bone

watch dial painters

bone sarcoma / head carcinoma

leukemia / red bone marrow

URANIUM HEALTH EFFECTS

bone

kidney

uptake 1 to 20%

use radium as surrogate

URANIUM

$$\text{DWEL*} = \frac{(\text{NOAEL})(\text{animal } f_1)(\text{adult weight})}{(\text{safety factor})(\text{water consumption}/\text{day})(\text{human } f_1)}$$

$$\text{DWEL} = \frac{(1\text{mg}/\text{kg}/\text{day})(0.01)(70\text{kg})}{(100)(2\text{L}/\text{day})(0.05)}$$

DWEL = 60 micrograms/L or 40 pCi/L

* Drinking Water Equivalent Level

RADON HEALTH EFFECTS

lung cancer

hard rock miners
   Colorado, Czechoslovakia, Sweden,
   Newfoundland

support from animal studies

242
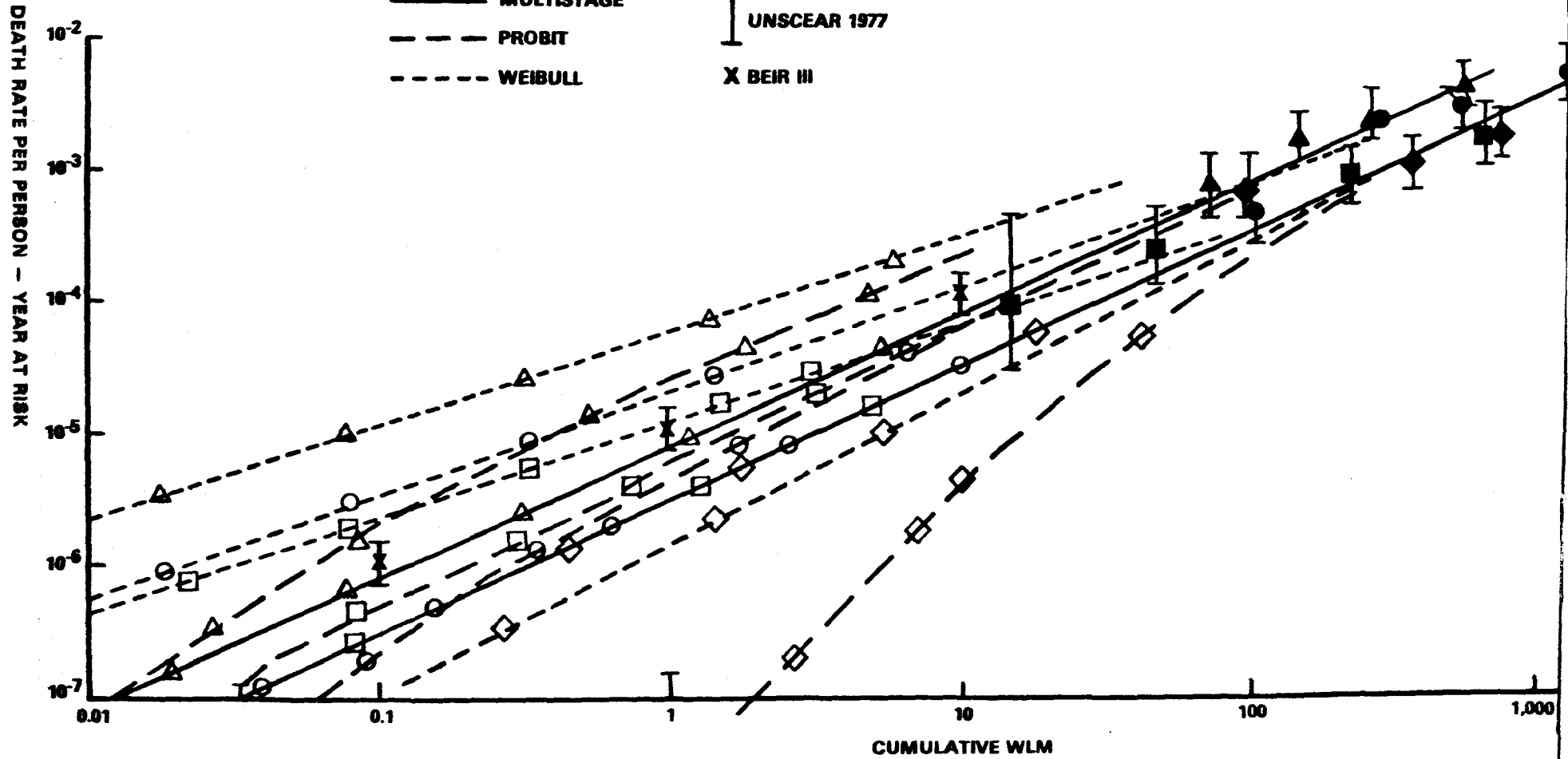
cause	annual number of fatal lung cancers
active smoking	100,000
passive smoking	5,000
radon	
- soil	5,000 to 20,000
- drinking water	100 to 1,500

RADIONUCLIDES RISK CALCULATIONS: EXAMPLES

Population Risk = occurrence in drinking water X cancer risk rate

X U.S. population

Radium

$(0.3 - 0.8)$ pCi/l X $(2.2 - 35)$ X 10^{-6} excess cases/lifetime/person/pCi/l

X 216 X 10^6 people

= 200 - 4000 excess cases/lifetime in the U.S.

Radon

$(50 - 300)$ pCi/l X $(0.2 - 60)$ X 10^{-7} excess cases/lifetime/person/pCi/l

X 216 X 10^6 people

= 2000 - 40,000 excess cases/lifetime in the U.S.

POPULATION RISK FOR RADIONUCLIDES
IN DRINKING WATER

Radionuclide	Estimates of Lifetime Population Risk (number of fatal cancers due to current exposures in drinking water)
Radium-226	200-4,000
Radium-228	200-4,000
Uranium-natural	40-1,000
Radon-222	2,000-40,000
Strontium-90	60-130
Lead-210	<100
Polonium-210	<300
Thorium-230	< 20
Thorium-232	< 4

RADON

absolute risk	$(3.8 - 15.2) \times 10^{-4}$ / WLM
months to years	12 - 24 months / years
WL to pCi/La	1 WL / 100 pCi/La
water to air transport	$(0.17 - 3.5) \times 10^{-4}$ La/Lw
non-equilibrium	0.3 - 0.7
years / lifetime	70 years / lifetime
occurrance	200 - 600 pCi/Lw
population	216×10^{6} people
TOTAL	4,000 - 150,000 per lifetime or 50 - 2,000 per year

SOME POPULATION RISK RATE BENCH MARKS

CAUSE	FATALITIES/YEAR (ORDER OF MAGNITUDE)
LUNG CANCER	100,000
RADON IN HOMES	10,000
RADON IN DRINKING WATER	1,000
COKE OVENS	100
BENZENE IN AIR	100
VINYLCHLORIDE IN AIR	
BEFORE REGULATION	10
AFTER REGULATION	1
CADMIUM IN AIR	10
ARSENIC IN AIR	10
VOLATILE ORGANIC CHEMICALS IN DRINKING WATER (TOTAL)	10

SUMMARY OF RISK LEVELS FOR RADIOACTIVITY IN DRINKING WATER

Estimated lifetime risk level	Annual effective dose equivalent (mrem/year)	226_{Ra} pCi/l	228_{Ra} pCi/l	U_{nat} pCi/l	222_{Rn} pCi/l
10^{-3}	100	100	200	700	10,000
10^{-4}	10	10	20	70	1,000
10^{-5}	1	1	2	7	100
10^{-6}	0.1	0.1	0.2	0.7	10

OCCURRENCE OF RADIUM-226
IN DRINKING WATER

Lifetime Risk Level	Radium-226 Concentration (pCi/l)	Annual Effective Dose Equivalent (mrem/yr)	Number of Public Drinking Water Supplies That Exceed the Concentration in Column 2
10^{-3}	100	100	1-10
10^{-4}	10	10	30-300
10^{-5}	1	1	300-3,000
10^{-6}	0.1	0.1	Below detection

OCCURRENCE OF RADIUM-228
IN DRINKING WATER

Lifetime Risk Level	Radium-228 Concentration (pCi/l)	Annual Effective Dose Equivalent (mrem/yr)	Number of Public Drinking Water Supplies That Exceed the Concentration in Column 2
10^{-3}	100	200	1-10
10^{-4}	10	20	30-100
10^{-5}	1	2	300-3,000
10^{-6}	0.1	0.2	Below detection

OCCURRENCE OF URANIUM
IN DRINKING WATER

Lifetime Risk Level	Uranium Concentration (pCi / l)	Annual Effective Dose Equivalent (mrem / yr)	Number of Public Drinking Water Supplies That Exceed the Concentration in Column 2
10^{-3}	700	100	1 - 10
10^{-4}	70	10	20 - 500
10^{-5}	7	1	100 - 2,000

OCCURRENCE OF RADON
IN DRINKING WATER

Lifetime Risk Level	Radon Concentration (pCi/l)	Number That Exceed the Concentration in Column 2	
		Public Drinking Water Supplies	Population (thousands)
10^{-3}	10,000	500-4,000	20-300
10^{-4}	1,000	1,000-10,000	200-4,000
10^{-5}	100	5,000-30,000	10,000-100,000
10^{-6}	10	10,000-40,000	50,000-100,000

ANALYTICAL METHODS FOR RADIONUCLIDES

Radium

Alpha-Emitting
Radium Isotopes
(Method 903.0)

Radium-226-Radon
Emanation Technique
(Method 903.1)

New York State
Department of
Health
(Ra-226 and -228)

Total Radium
(Method 304)

Radium-226
(Method 305)

Coincidence
Spectrometry

Gamma Ray
Spectrometry
(Ra-226 and -288)

Solid State Nuclear
Track Detector

Radiochemical
Determination of
Ra-226 in Water
Samples
(Method Ra-03)

Radiochemical
Determination of
Ra-228 in Water
Samples
(Method Ra-05)

Ra-228 by Liquid
Scintillation
Counting
(Method 904.1)

Radium-228
(Method 904.0)

ANALYTICAL METHODS FOR RADIONUCLIDES
(Continued)

Gross Alpha Particle Activity

**Gross Alpha and
Gross Beta
Radioactivity
(Method 900.0)**

**Gross Radium
Alpha Screening
Procedure
(Method 900.1)**

**Gross Alpha
Activity in
Drinking Water
by Coprecipitation
(Method 00-02)**

**Gross Alpha and Beta
(Method 703)**

**Gross Alpha Particle
Activity
(Method D-1943)**

Gross Beta Particle Activity

**Gross Alpha and
Beta Radioactivity
(Method 900.0)**

**Gross Beta Particle
Activity
(Method D-1890)**

ANALYTICAL METHODS FOR RADIONUCLIDES
(Continued)

Uranium

Radiochemical
(Method 908.0)

Fluorometric
(Method 908.1)

Laser Induced
Fluorometry
(Method 908.2)

ASTM Method
D-2907

Man-made Radionuclides

Radioactive
Cesium
(Method 901.0)

Gamma Emitting
Radionuclides
(Method 901.1)

Radioactive
Iodine
(Method 902.0)

Radioactive
Strontium
(Method 905.0)

Tritium
(Method 906.0)

Strontium 89, 90
(Method 303)

Tritium
(Method 306)

Gamma Ray Spectroscopy
(Method D-2459)

Radon

Liquid Scintillation
(including modification
using mineral oil so
sample can be mailed)

Solid State Nuclear
Track Detector

Lucas Cell

COSTS OF ANALYTICAL METHODS

radium-226	$100
radium-228	$100
uranium	$ 25
radon	$ 25
gross alpha	$ 25
gross beta	$ 25

RADIONUCLIDE TREATMENT METHODS

Radium

> lime softening
>
> reverse osmosis
>
> iron and manganese
>
> ion exchange

Uranium

> anion exchange
>
> lime softening (high pH)
>
> reverse osmosis

Radon

> aeration
>
> granular activated carbon

Man-Made

> ion exchange

COSTS IN CENTS / 1000 GALLONS FOR CONTROLLING RADIUM IN DRINKING WATER (MID 1982 DOLLARS)

		Population Served	
Treatment Methods	Removal Eff. %	100- 500	10,000- 100,000
Coagulation / Filtration*	>75	28	7
Lime Softening*	>85	-	10
Ion Exchange (anion)	>95	210	160
Ion Exchange (cation)	>90	80	33
Iron and Manganese	<40	110	30
Lime Softening - new	<90	-	50
Reverse Osmosis	>90	320	160

*Modified in existing facility.

COSTS FOR REMOVING RADON FROM DRINKING WATER BY PACKED TOWER AERATION (99% REMOVAL)

	Population Served		
	100-500	3,300-10,000	75,000-100,000
Total Capital Cost ($1,000)	67	250	2,200
O&M Cost ($1,000 per year)	1.2	15	230
Cost ¢/1,000 gallons	75	14	9

POINT OF USE: RADON TREATMENT
COSTS GAC (200gpd)

Influent Radon pCi/l	Effluent Radon pCi/l	Capital Costs $	Operating Costs $/year
15,000	1,350-3,300	$430-760	$20
30,000	2,700-6,600	$430-760	$20
150,000	1,200	$1,500	$40

POINT OF USE: RADON TREATMENT
COSTS AERATION (200gpd)

Influent Radon pCi / l	Effluent Radon pCi / l	Capital Costs $	Operating Costs $ / year
15,000	750	$ 900	$60
30,000	1,500	$ 900	$80
150,000	<7,500	$1,000	$80

MAN MADE RADIONUCLIDES

approximately 2,000

limit to 200 due to
- half life
- solubility
- pharmacokinetics
- health effects

fission fragments

transuranics

PART IV

RISK MANAGEMENT

A. OVERVIEW OF RISK MANAGEMENT AND CONTROL STRATEGIES

Scope: Provide an overview of risk management and the alternatives
available for controlling contaminants in drinking water.
While the scope of this talk does not include EPA's
existing and proposed regulations, questions concerning
the technology portions of these regulations are invited.

A.   RISK MANAGEMENT

   1.   Definition -- The process of deciding what to do about
        a problem.

   2.   Involves a broader array of disciplines than risk
        assessment (which is finding out what the problems are).

   3.   Assumes knowledge of health risks.

   4.   Factors in feasibility, cost, and reexamines exposure
        issues previously dealt with in risk assessment.

   5.   Done on a national level through drinking water standards
        (maximum contaminant levels), but can be carried out on
        a local level for cleanup of unregulated contaminants.

B.   TWO IMPORTANT CONCEPTS

   1.   Chemicals degrade in the environment -- sometimes the
        intermediate products are more toxic (e.g., tetrachloro-
        ethylene to vinyl chloride).

   2.   For some chemicals (esp., carcinogens) measurement
        becomes a constraint on treatment goals (maximum contami-
        nant levels).

        Two concepts:
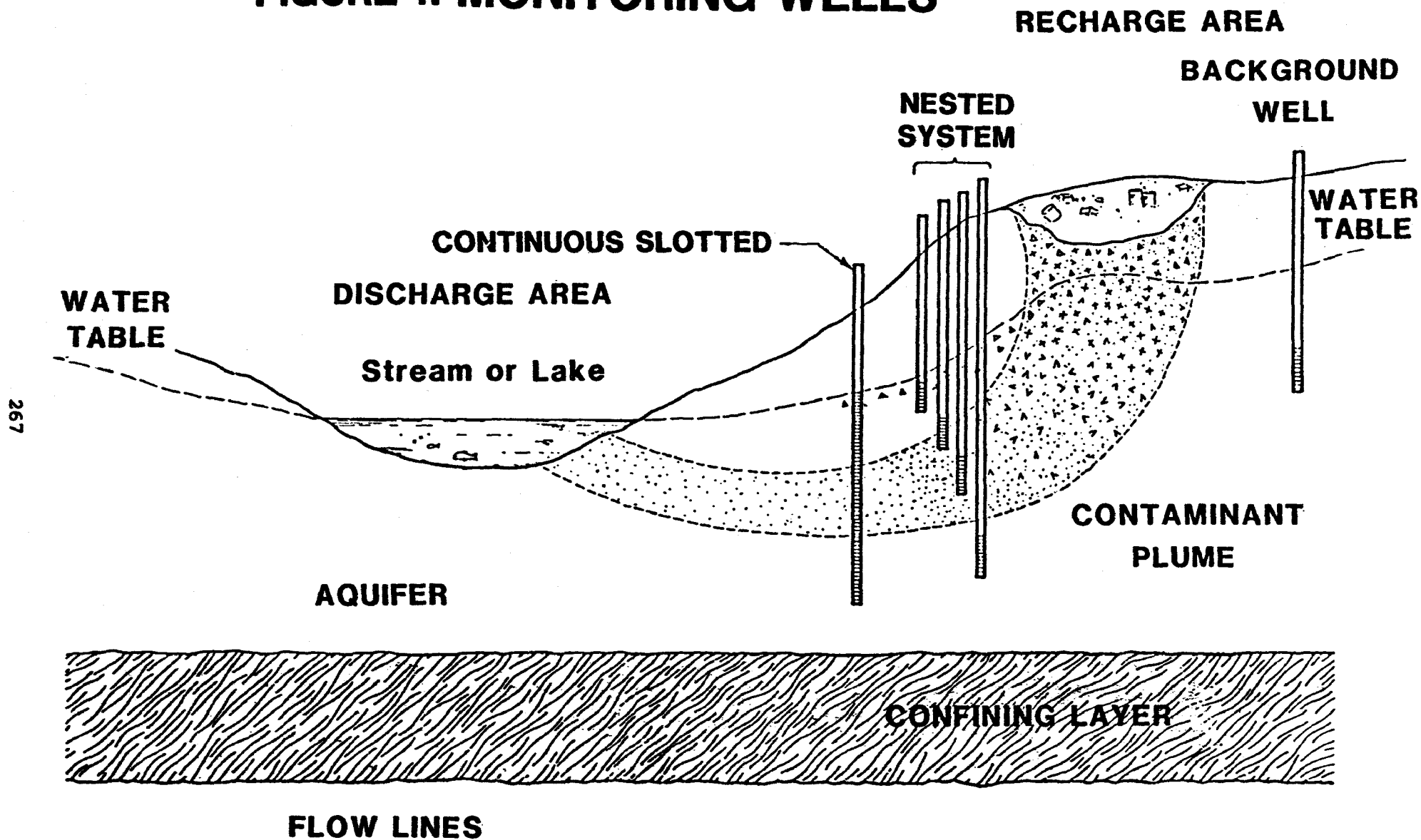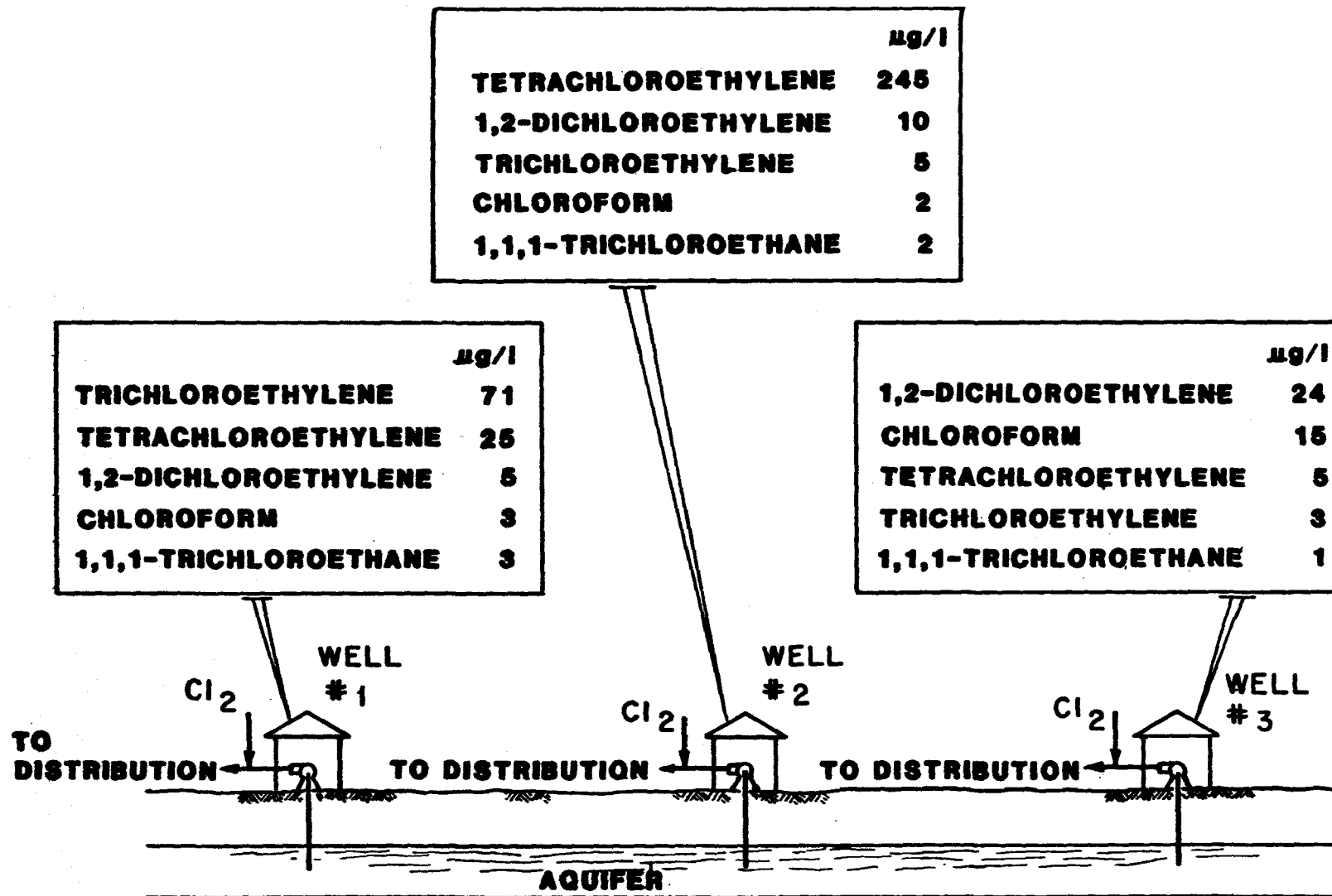
        a.   minimum detection limit (MDL):   99% assurance the
             value is not zero.

        b.   practical quantification limit (PQL):   generally,
             5 to 10 times the MDL -- this is a concentration at
             which a sufficient number of laboratories can report
             results within a reasonable range of the true value
             (say, ±20 to 40%).

C. OVERALL APPROACH

1. Development of a reliable data base.

    a. Routine monitoring.
    b. Utilize other existing nearby wells for more comprehensive monitoring, e.g., private/industrial/ abandoned.
    c. Supplemental monitoring wells. (Figure 1)
    d. Existing hydrogeologic data.

2. Use data base to understand situation.

    a. Model ground water in attempt to determine location of source.
    b. Project future conditions, e.g., impact of continued pumping, impact of stopping pumping.

3. Recognize that the most cost effective treatment solutions are site-specific.

    a. Dual utilization of existing facilities (e.g., air stripping in existing reservoirs).
    b. Impact on system hydraulics.
    c. Energy considerations.

4. General considerations. (Figure 2)

    a. Type of contaminant:
       - inorganic
       - organic
       - other water quality data

    b. Contaminant levels:
       - historical levels
       - mix of contaminants
       - design influent levels
       - design effluent levels

    c. Characteristics of water supply:
       - surface or ground water
       - number of wells
       - location of wells
       - system configuration (reservoir, booster pumps)

    d. Safety:
       - plant operators
       - community
       - consumers

    e. Costs:
       - capital
       - operating

FIGURE 1: MONITORING WELLS

RECHARGE AREA

BACKGROUND WELL

NESTED SYSTEM

WATER TABLE

CONTINUOUS SLOTTED

DISCHARGE AREA

Stream or Lake

WATER TABLE

CONTAMINANT PLUME

AQUIFER

CONFINING LAYER

FLOW LINES

267

FIGURE 2: EXAMPLE OF
A CONTAMINATED GROUND WATER SUPPLY
SMALLTOWN, U. S. A.

f.　Reliability:
　　　　　- simplicity
　　　　　- back-up
　　　　　- standard equipment
　　　　　- training

D.　BASIC CATEGORIES OF CONTROL STRATEGIES

　　1.　Source Control Strategies -- controlling raw water
　　　　source to reduce concentration or eliminate compound.

　　　　a.　Eliminate contaminant source.
　　　　b.　Locate new source of supply or reduce demand.
　　　　c.　Blend existing new sources.
　　　　d.　Operate interceptor well.

　　2.　Treatment Strategies -- involves the use of a treatment
　　　　technique to reduce concentrations in the water supply.

　　　　a.　Inorganics Removal Processes

　　　　　　- conventional treatment
　　　　　　- lime softening
　　　　　　- ion exchange
　　　　　　- reverse osmosis
　　　　　　- activated alumina
　　　　　　- electrodialysis

　　　　b.　Organics Removal Processes

　　　　　　- conventional treatment
　　　　　　- aeration (diffused air, packed column, slat-tray)
　　　　　　- adsorption (GAC, PAC, resins)
　　　　　　- biodegradation
　　　　　　- reverse osmosis
　　　　　　- oxidation
　　　　　　- boiling

　　3.　Combined Strategies -- involves the use of a combination
　　　　of a source control strategy and a treatment strategy.

　　4.　Short-term Strategies -- bottled water or point-of-use
　　　　treatment.

E.　ELIMINATE CONTAMINANT SOURCE

　　1.　Involves identification of the contaminant source and,
　　　　subsequently, eliminating the source.

　　2.　Example - source is a leaking underground storage tank;
　　　　fix or remove tank; pump well to waste until contaminant
　　　　concentration drops.

3. Disadvantages of this control strategy:

- Sources of the compound may not always be easily
determined because chemicals can migrate long
distances from the source to a well.

- Size of the affected supply and the degree of
infiltration may be such that many years would be
required to purge the supply even after the source
is identified and eliminated.

F. LOCATE NEW SOURCE OF SUPPLY OR REDUCE DEMAND

1. Involves abandoning the affected well(s) and locating
an alternative supply source or reducing water demand.

2. New supply source may be:

- new well in an unaffected aquifer. (Figure 3)
- tap surface supply source.
- purchase water from a neighboring community.

3. Disadvantages with this control strategy are:

- An unaffected source of supply may not be available
nearby, and the cost of developing a new source
which is far removed from the service area may be
prohibitive.

- Developing a new ground water supply may not eliminate
the potential of the compound migrating to the new
supply.

- A neighboring community's supply may not be capable
of providing additional water to replace a large
affected supply.

G. BLENDING EXISTING AND/OR NEW SOURCES

1. Involves blending water from several wells, to reduce
the concentration of the compound via dilution.

2. Figure 4 illustrates three examples of blending:

- Blend water from one affected well and two unaffected
wells.

- Blend water from three affected wells and treat at
one location.

- Blend water from two unaffected wells with treated
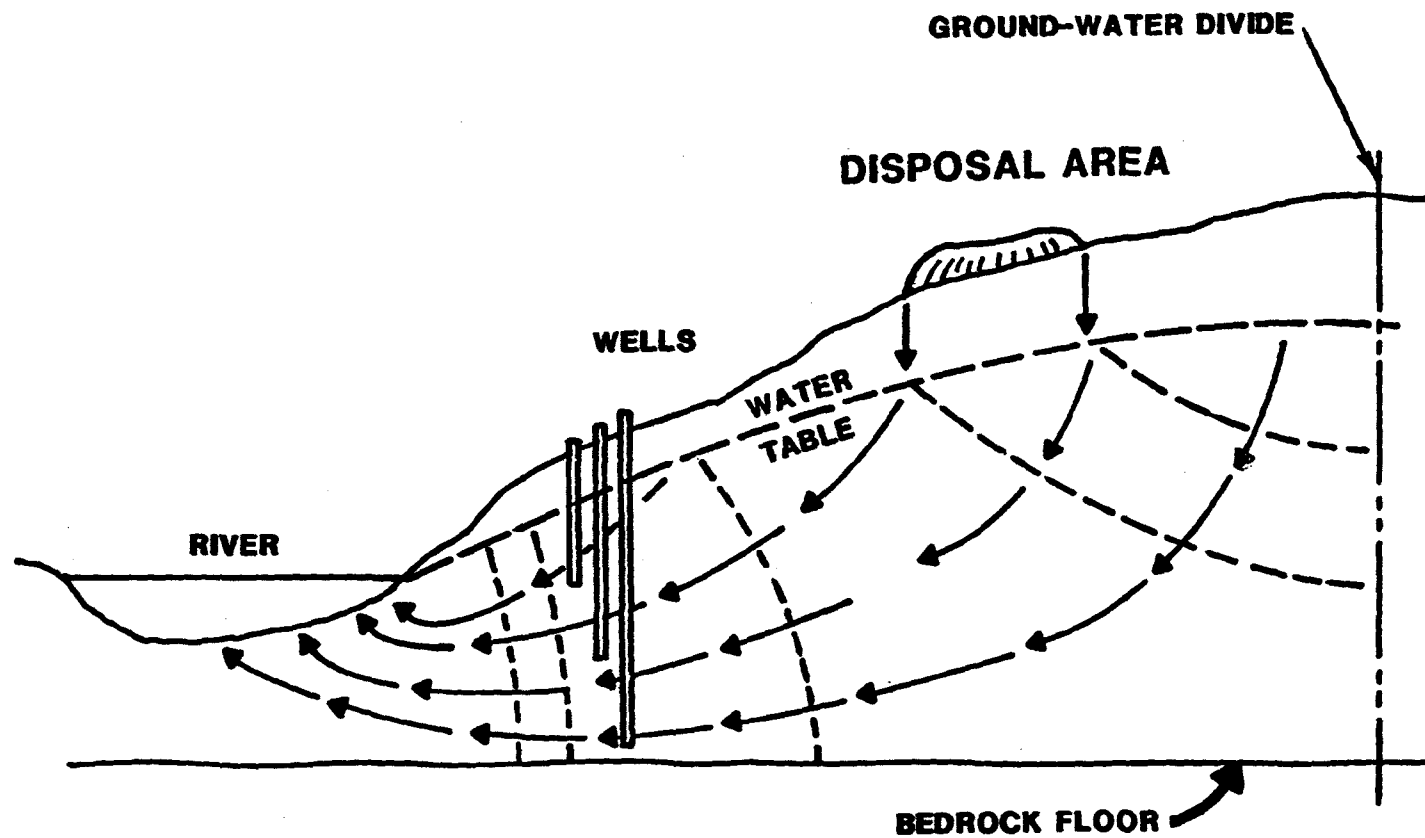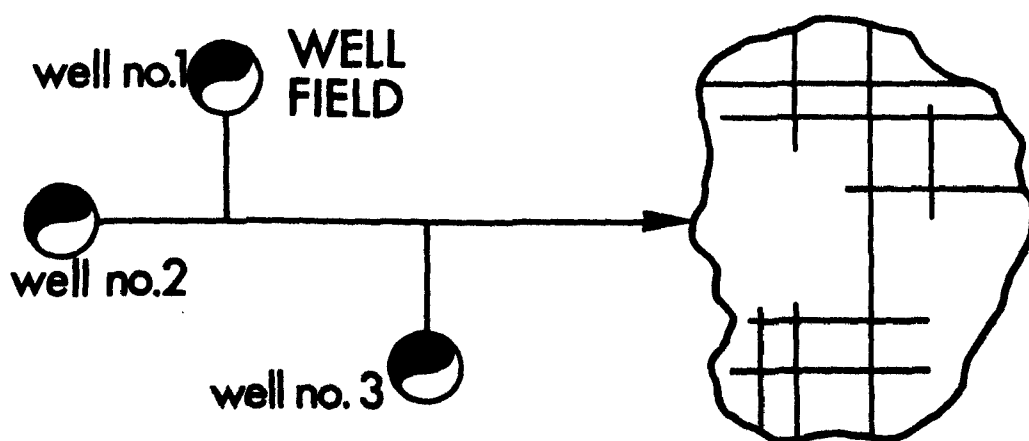water from an affected well.

GROUND-WATER DIVIDE

DISPOSAL AREA

WELLS

WATER TABLE

RIVER

BEDROCK FLOOR

FIGURE 3: DRILL NEW WELL

FIGURE 4: BLENDING EXISTING SOURCES

well no.1 WELL FIELD

well no.2

well no. 3

3. Disadvantages of this control strategy are:

- The ground water system may not be flexible enough to permit sufficient blending.

- The contaminant concentrations may be too high to achieve an acceptable level via dilution.

- Consumers may not accept this alternative because it does not involve removal of the compound from the water.

H. OPERATE INTERCEPTOR WELL

1. Involves pumping a well(s) to waste which is "upstream" from other wells in the system, removing the chemical from the aquifer before the water reaches the "good" wells. (Figure 5)

2. Currently being used in several locations. Without interceptor wells operating, compound levels are between 50 and 100 ug/L. With interceptor wells operating, levels drop to less than 50 ug/L.

3. Disposal of "wastewater" from interceptor well may be a problem.

I. SHORT TERM STRATEGIES TO REDUCE EXCESSIVE RISKS

1. Bottled Water.

- Home delivery.

- Central pickup.

- Quality -- should meet all MCLs.

- Cost -- home delivery approximately $50 per month.

2. Point-of-Use Devices.

- Definition -- treats water at a single tap.

- Many types available -- activated alumina, granular activated carbon, reverse osmosis, etc.

- Not recommended for waters with microbiological contamination (esp., excessive turbidity).

- Suitable for reducing risks of exposure for short-term emergencies.

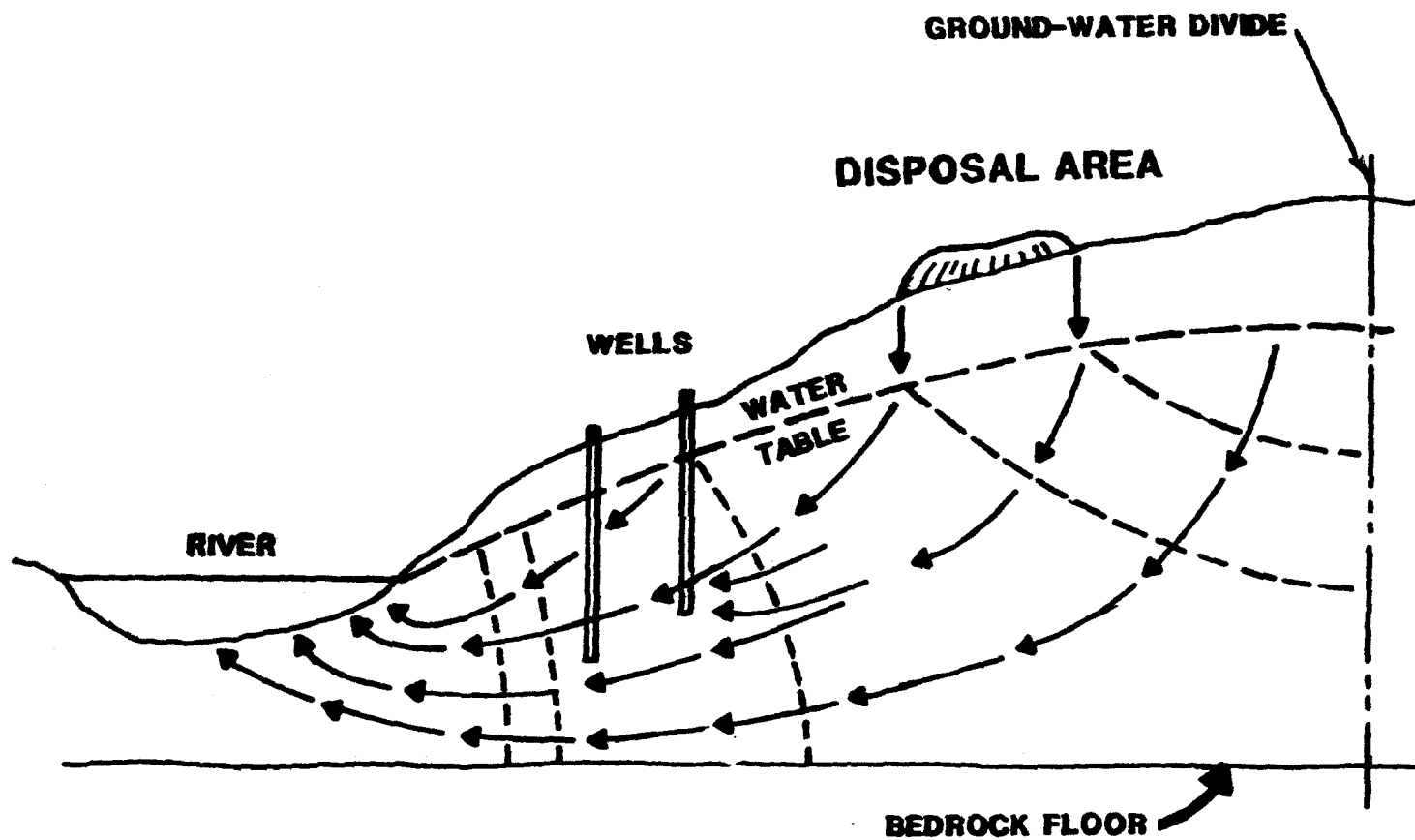- Costs: $20-$60 per month per household.

273

FIGURE 5: INTERCEPTOR WELL

FIGURE 6: POINT-OF-USE-DEVICES
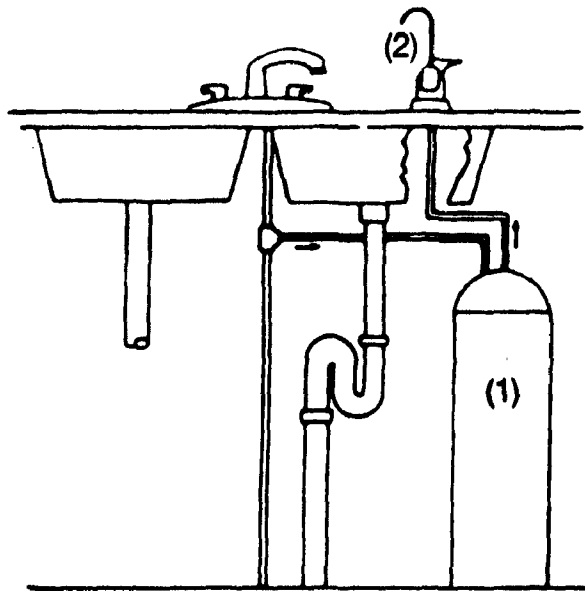
LEGEND
1. ION EXCHANGE
2. DRINKING WATER FAUCET

ION EXCHANGE TREATMENT UNIT
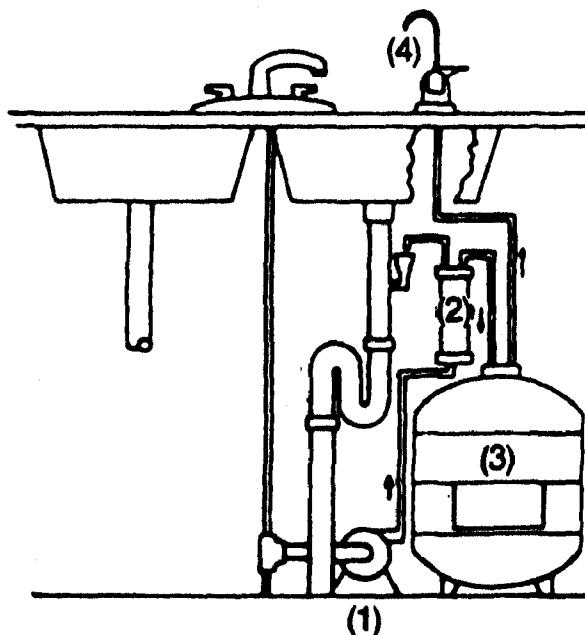
LEGEND
1. BOOSTER PUMP
2. REVERSE OSMOSIS MODULE
3. WATER STORAGE TANK
4. DRINKING WATER FAUCET

REVERSE OSMOSIS TREATMENT UNIT

J. CONCLUSIONS

1. Understand the hydrogeology of your supply systems.

2. Evaluate present and probable future contaminant concentrations.

3. Determine and evaluate alternative control strategies.

   - short- (Figure 6) and long-term (Figure 7) strategies.
   - capital and operating costs. (Figure 8)
   - time required to implement.

WELL AERATOR CORROSION INHIBITOR DISTRIBUTION SYSTEM

F

2 WELLS Cl$_2$ NaoH
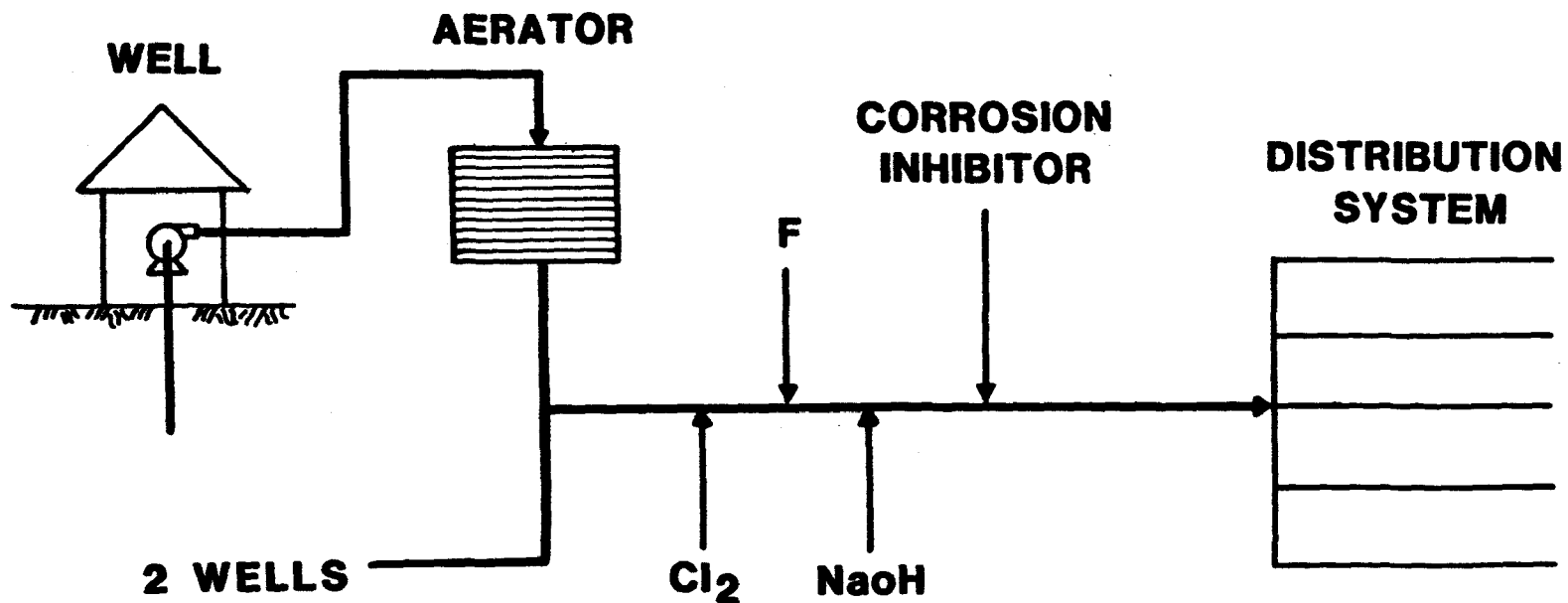
FIGURE 7: NORWALK, CT. ORGANICS
REMOVAL SYSTEM
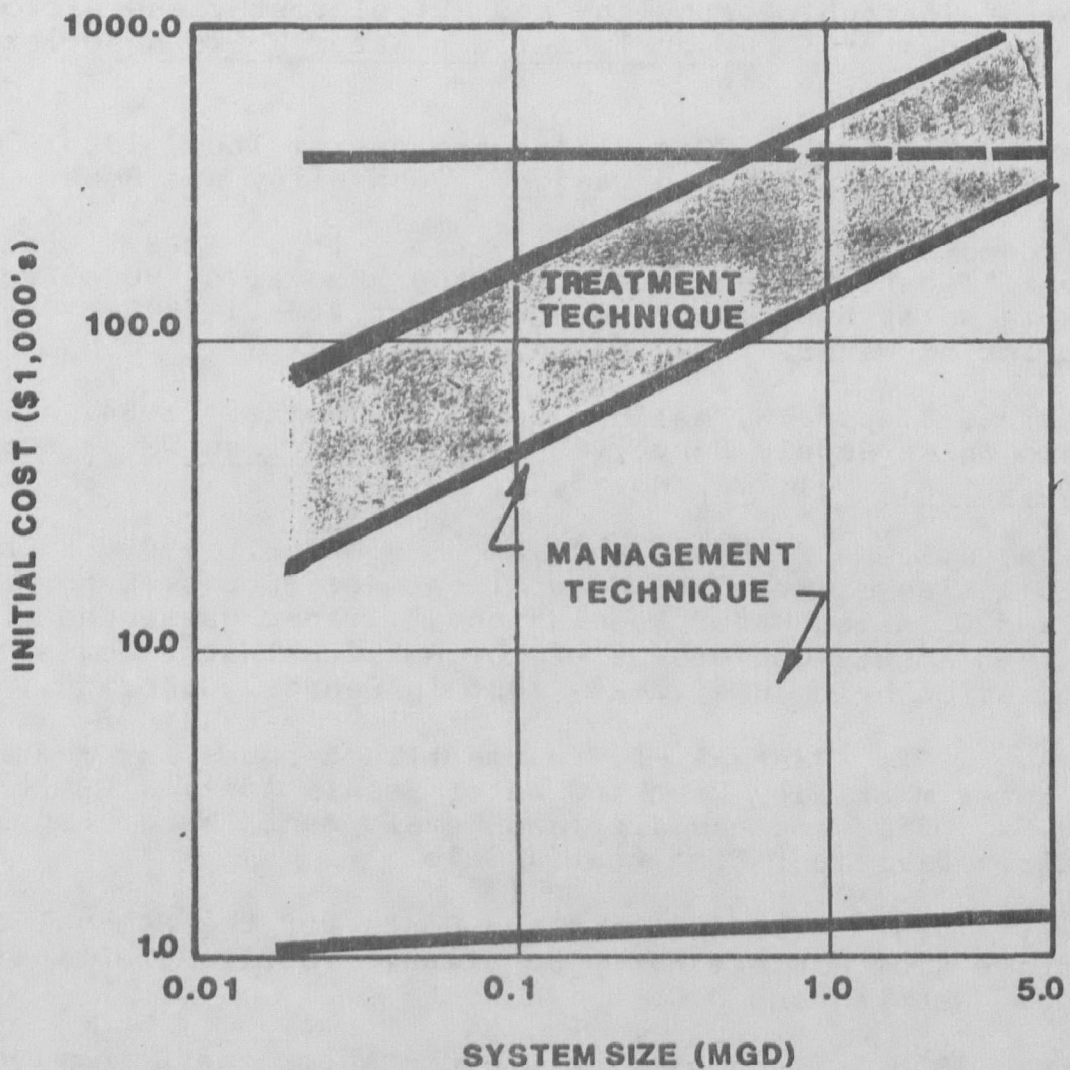
FIGURE 8: COMPARISON OF COSTS
FOR VOC CONTROL ALTERNATIVES

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6. Dyksen, J.E., A.F. Hess, and J.K. Schaeffer. 1986. "The Capabilities of Standard Water Treatment Processes to Meet Revised Drinking Water Regulations." Paper presented at the 1986 Annual Conference of the American Water Works Association held June 22-26, 1986 in Denver, Colorado.

7. USEPA. 1978. "Manual of Treatment Techniques for Meeting the Interim Primary Drinking Water Regulations." EPA 600/8-77-005. Office of Research and Development, Water Supply Research Division, Cincinnati, Ohio.

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B.

INORGANICS TREATMENT

OVERVIEW AND CASE STUDIES

I. CONVENTIONAL TREATMENT
    LIME SOFTENING
    REVERSE OSMOSIS

II. ION EXCHANGE

III. ACTIVATED ALUMINA

IV. PROCESS SELECTION

I. CONVENTIONAL TREATMENT, LIME SOFTENING AND REVERSE OSMOSIS

Scope: Provide a review of the use of conventional, lime softening and reverse osmosis treatment technologies for removing inorganics from drinking water supplies, including process design considerations and limitations. Provide case studies of conventional treatment and reverse osmosis systems for inorganics removal.

A. Conventional Treatment

1. Process used for the removal of color and turbidity in surface waters. Inorganic removal occurs through absorption or enmeshment in the floc. A process schematic is presented as Figure I-1.

2. Typical processes include:

   - Raw water pumpage

   - Flash mixing with coagulants such as alum, ferric salts or cationic/anionic polymers

   - Flocculation

   - Sedimentation

   - Filtration

   - Disinfection

   - Storage and distribution

3. Process design considerations:

   - pH
   - Coagulant aids

4. The process is generally effective for the treatment of the following inorganic species:

   Alum Coagulation: Good to Excellent for

       AS(V)...at pH below 7.5
       Cd......at pH above 8.5
       Cr(III)
       Pb
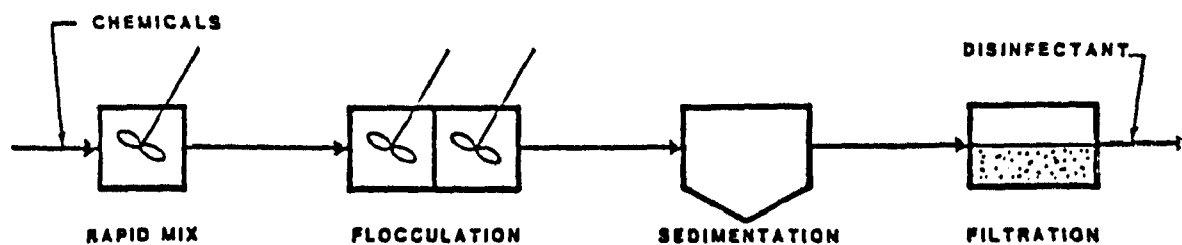   Ag......at pH below 8

   Iron Coagulation: Good to Excellent for

FIGURE 1-1

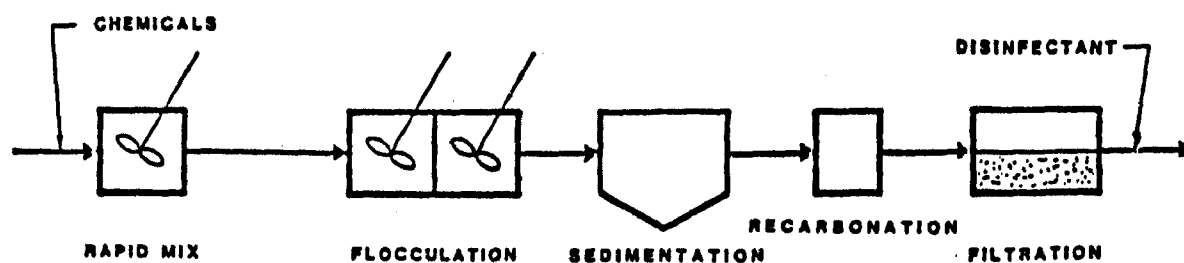FIGURE – SCHEMATIC OF
COAGULATION/FILTRATION PROCESSES

FIGURE – SCHEMATIC OF
LIME SOFTENING PROCESSES

As(V)
Cd......at pH above 8
Cr(III)
Cr(VI)..with ferrous salts
Pb
Ag

5. Limitations: In general, this process is effective in removing many of the cationic inorganic chemicals. For nitrate, nitrite, barium and sulfate the process is virtually ineffective.

B. Case Study: Conventional Treatment -- Northeastern Illinois

1. Background Information:

    a. System Characteristics:

        1) Ground water supply.

        2) Small regional areas of barium contamination, as illustrated on Figure I-2.

        3) Contaminated water drawn from Cambrian-Ordovician Aquifer.

        4) No barium contamination where sulfate >50 mg/L.

    b. Water Quality:

        1) Barium: 0.4 - 8.5 mg/L

    c. Maximum Contaminant Level:

        1) Barium: 1.0 mg/L

2. Treatability Tests, Chemical Precipitation - Direct Filtration:

    a. Test Description:

        1) 500 ml jar tests
        2) Gravity filtration with paper filters
        3) Initial Barium concentration: 7.4 mg/L
        4) Chemicals tested:

Chemical	Operational Purpose
Alum	Coagulant-precipitant
Sulfuric acid	pH adjustment-precipitant
Hydrochloric acid	pH adjustment
Sodium hydroxide	pH adjustment
Potassium hydroxide	pH adjustment
Calcium hydroxide	Precipitant-pH adjustment

283

BARIUM CONTAMINATION – NORTHEASTERN ILLINOIS
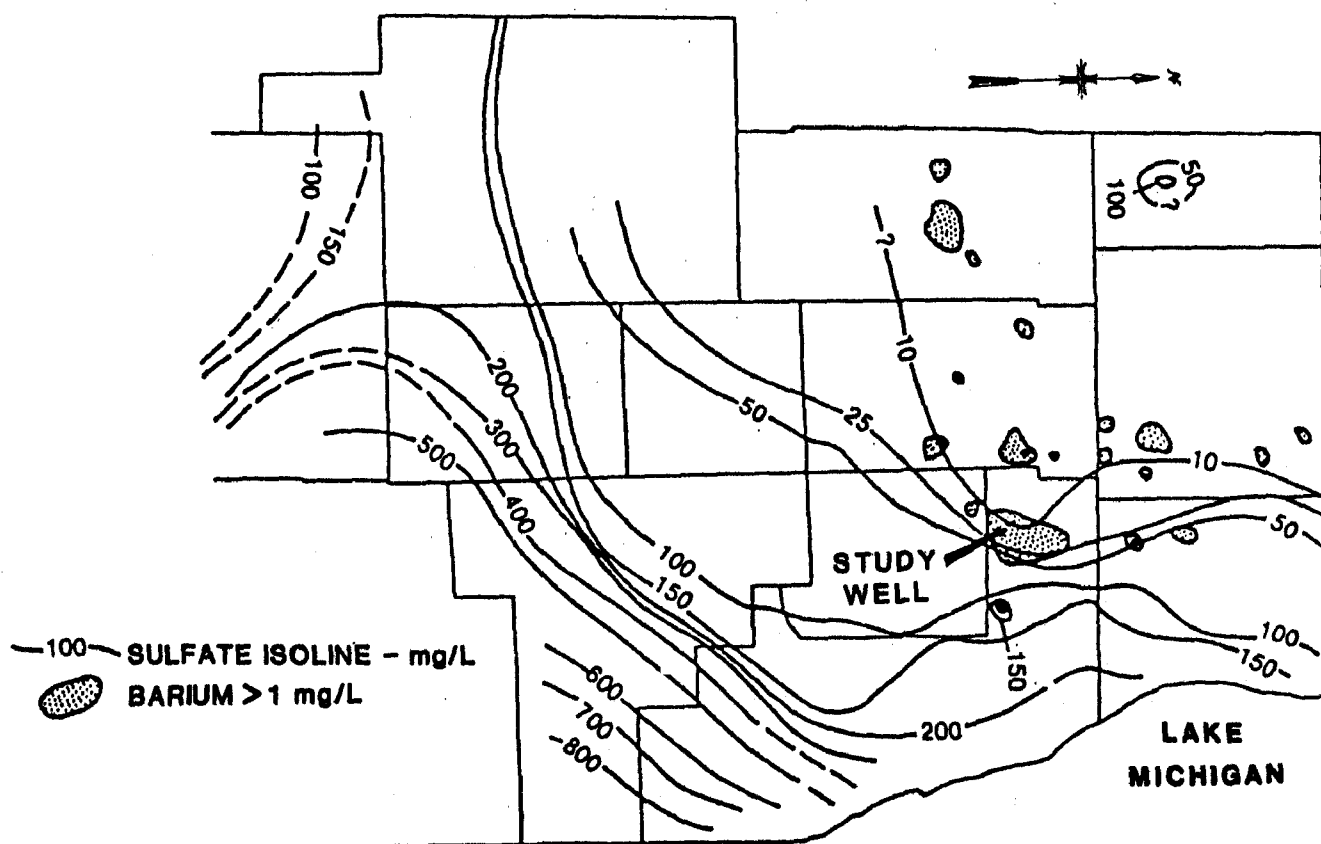
Chemical	Operational Purpose
Calcium sulfate (gypsum)	Precipitant
Ferrous sulfate	Coagulant-precipitant
Sodium bisulfate	Precipitant
Commercial gypsum	Precipitant
Anionic polymer	Flocculant-filter aid
Diatomaceous earth	Filter precoat

b. Test Results:

1) Optimum Barium removal using calcium sulfate (gypsum)
2) Optimum Dosage: 75 to 175 mg/L of gypsum
3) Optimum pH: = 11.0

3. Pilot Tests:

a. Pilot Plant Description:

1) Precipitation

2) Direct Filtration

3) Tested:

- 2 gypsum doses
- 3 anionic polymer filter aids
- Various raw water Barium concentrations

4) Pilot plant schematic shown on Figure I-3.

b. Results:

1) Reliable reduction of barium to acceptable levels

2) Barium reduction from 6 to 0.5 mg/L, or 91%

3) Chemical Dosages:

   Gypsum - 100 mg/L
   Polymer - 0.25 mg/L

c. Operating Parameters:

1) pH = 11.0
2) Filter loading = 1.5 gpm/ft^2

4. Cost Data-Full Scale Estimates:

a. Capacity = 1050 gpm = 1.5 MGD

PILOT PLANT SCHEMATIC
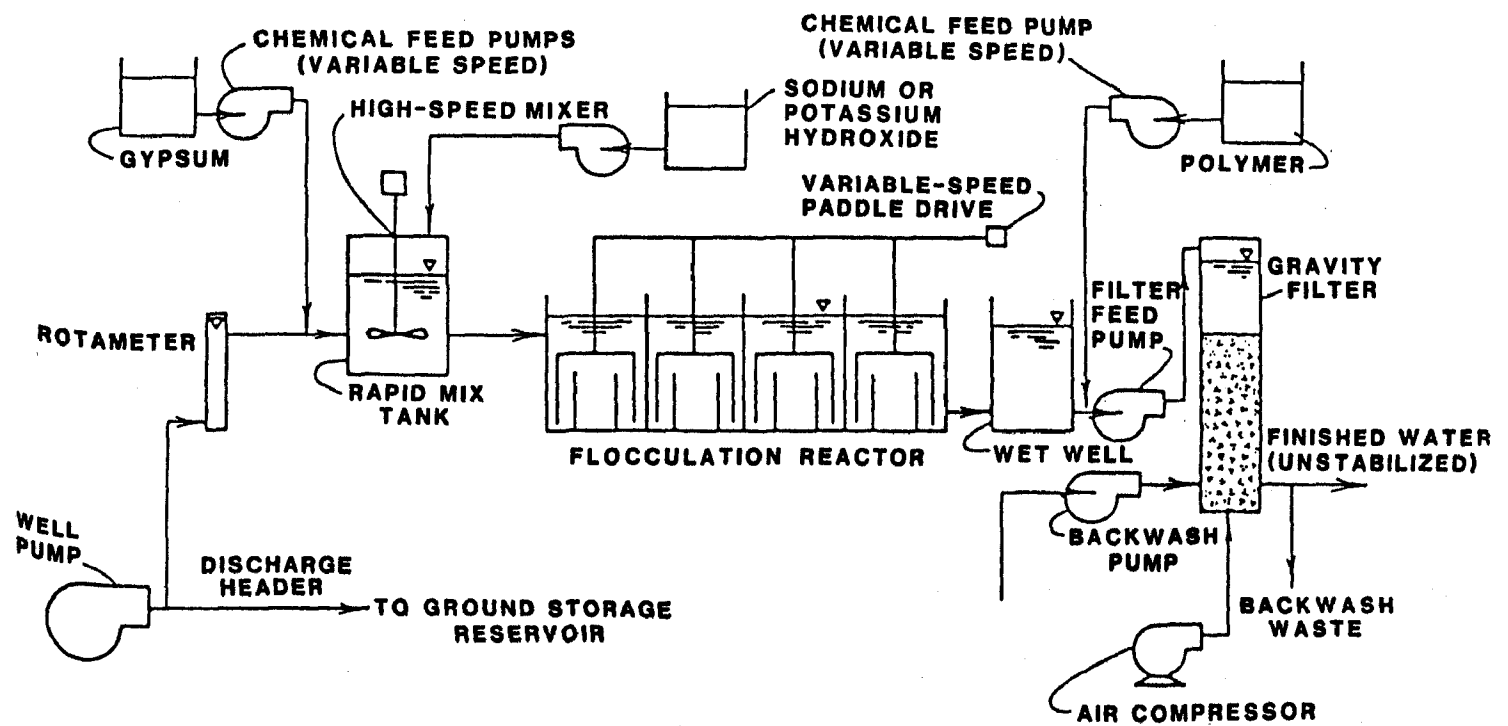
b.   Components:

       1)   Aerator
       2)   Rapid mix tank
       3)   Flocculation basin
       4)   Gravity filter
       5)   Recarbonation system
       6)   Transfer pumps
       7)   Potassium hydroxide system
       8)   Gypsum system
       9)   Polymer system
      10)   Appurtenances

c.   Costs (1980 dollars):

       1)   Construction costs: $1,068,100
       2)   Total capital costs: $2,366,000
       3)   Annual O&M costs: $ 155,900

C.   Lime Softening

   1.   Process used for the removal of hardness from ground and surface
        water. Inorganic chemical removal through floc absorption or
        enmeshment.

   2.   Typical unit processes include:

        -   Raw water pumpage
        -   Softening with lime and occasionally soda ash
        -   Sedimentation
        -   Filtration
        -   Disinfection
        -   Storage and distribution

   3.   Process design considerations:

        -   pH coagulants

   4.   This process is generally effective for the treatment of the follow-
        ing inorganic species:

   Good to Excellent for:

        As(V)...at pH = 10-10.8
        Ba......at pH = 9.5-10.8
        Cd
        Cr(III).at pH above 10.5
        Pb
        Ag

5. Limitations: In general the process is effective in removing cations and fluoride. The process does not effectively remove Cr (IV), nitrate, selenium or mercury.

D. Reverse Osmosis

1. Process used for the desalting of sea water or brackish ground waters. Inorganic chemicals are removed by retention in the brine by the membrane. Several types of membranes are available including spiral wound and hollow fiber with some membranes designated as high pressure (greater than 350 psi) or low pressure (below 250 psi). Examples of spiral wound and hollow fiber membranes are presented on Figure I-4. A process schematic is presented as Figure I-5.

2. Typical unit processes include:

    - Raw water pumpage
    - Pretreatment
    - Membrane desalination
    - Disinfection
    - Storage and distribution

3. Process design considerations:

    - Influent suspended solids
    - Competing ions
    - Ionic size
    - Membrane pore size
    - Membrane type

4. This process is generally effective for the treatment of the following inorganic species:

Good to Excellent for:

As(III)	Cd	F	Nitrate
As(V)	Cr(III)	Pb	Se(IV),(VI)
Ba	Cr(VI)	Hg	Ag

5. Limitations: The process is generally effective in removing all inorganic chemicals.

E. Case Study: Reverse Osmosis -- Sarasota County, Florida

1. Background Information

    a. System Characteristics

        - Ground water supply
        - Eight RO systems tested
        - Flow ranges 0.0008 to 1.0 mgd

288

FIGURE 1-4

TYPES OF REVERSE OSMOSIS MEMBRANES
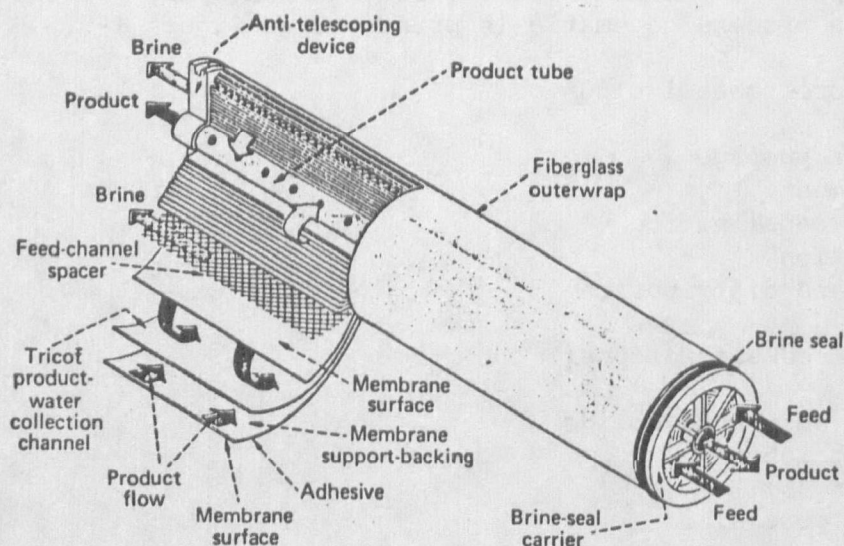
SPIRAL WOUND

HOLLOW FIBER

FIGURE 1-5

REVERSE OSMOSIS

RAW WATER

PRETREATMENT

REVERSE OSMOSIS
ELECTRODIALYSIS

DISINFECTION

BRINE
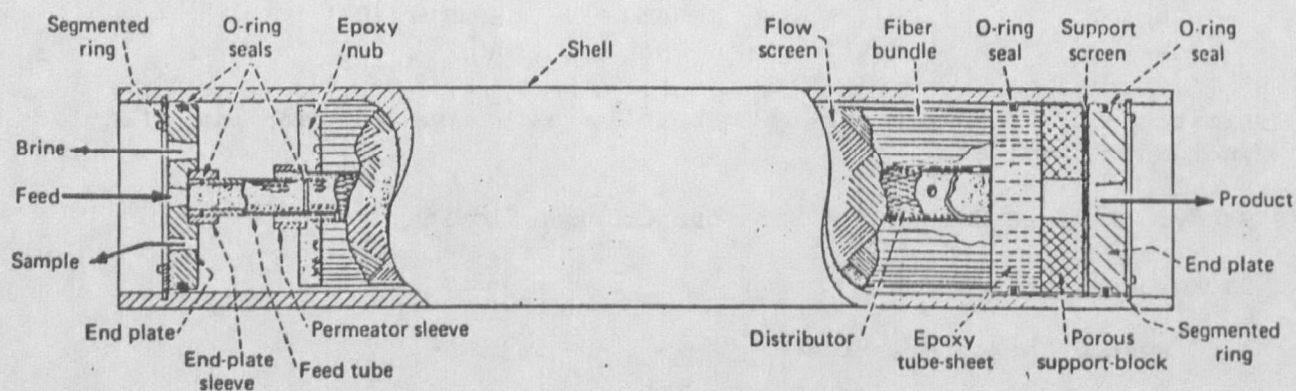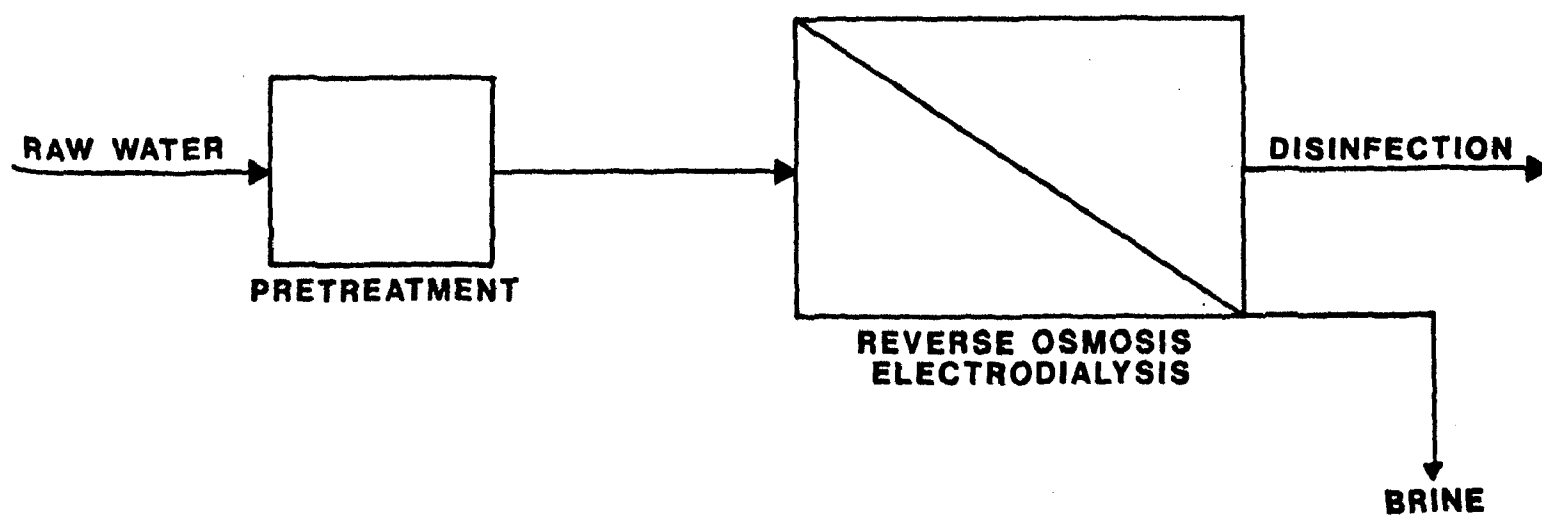
- Radium concentrations high due to phosphatic limestone

b. Water Quality

- Radium: 3.4 to 20.2 pCi/L

2. Plant Description

a. Plant Capacity: 800 to 1,000,000 gpd

b. Percent Recoveries: 28 percent to 54 percent

c. Operating Pressures: 200 psi to 425 psi

d. Membrane Type: Hollow Fiber & Spiral Wound

e. Treatment processes:

- Pretreatment

  - Cartridge filtration
  - pH adjustment
  - Ion sequestration

- Reverse Osmosis

- Posttreatment

  - pH adjustment
  - Degasification
  - Chlorination

f. Process schematic for a typical RO system is presented as Figure I-6.

3. Plant Performance

a. Raw Water Concentration: 3.2 - 20.2 pCi/L
b. Product Water Concentration: 0.14 - 2.0 pCi/L
c. Reject Water Concentration: 7.8 - 37.8 pCi/L
d. All product waters below regulatory limit of 5.0 pCi/L

4. Costs

a. Operating Costs: $0.60 - $1.54 per 1,000 gallons

b. Components:

- Chemicals
- Electrical power

FIGURE 1-6

TYPICAL RO SYSTEM

GENERATOR SET

HIGH SERVICE PUMPS

BRINE TO PERCOLATION POND

PERMEATORS

CONTROL PANEL AND PUMPS

PRODUCT TO DEGASIFIER AND RESERVOIR

PO$_4$ FEED

ACID FEED

FILTER

MIXING TANK

FEED

CLEANING SOLUTION

SODIUM SILICATE FEED
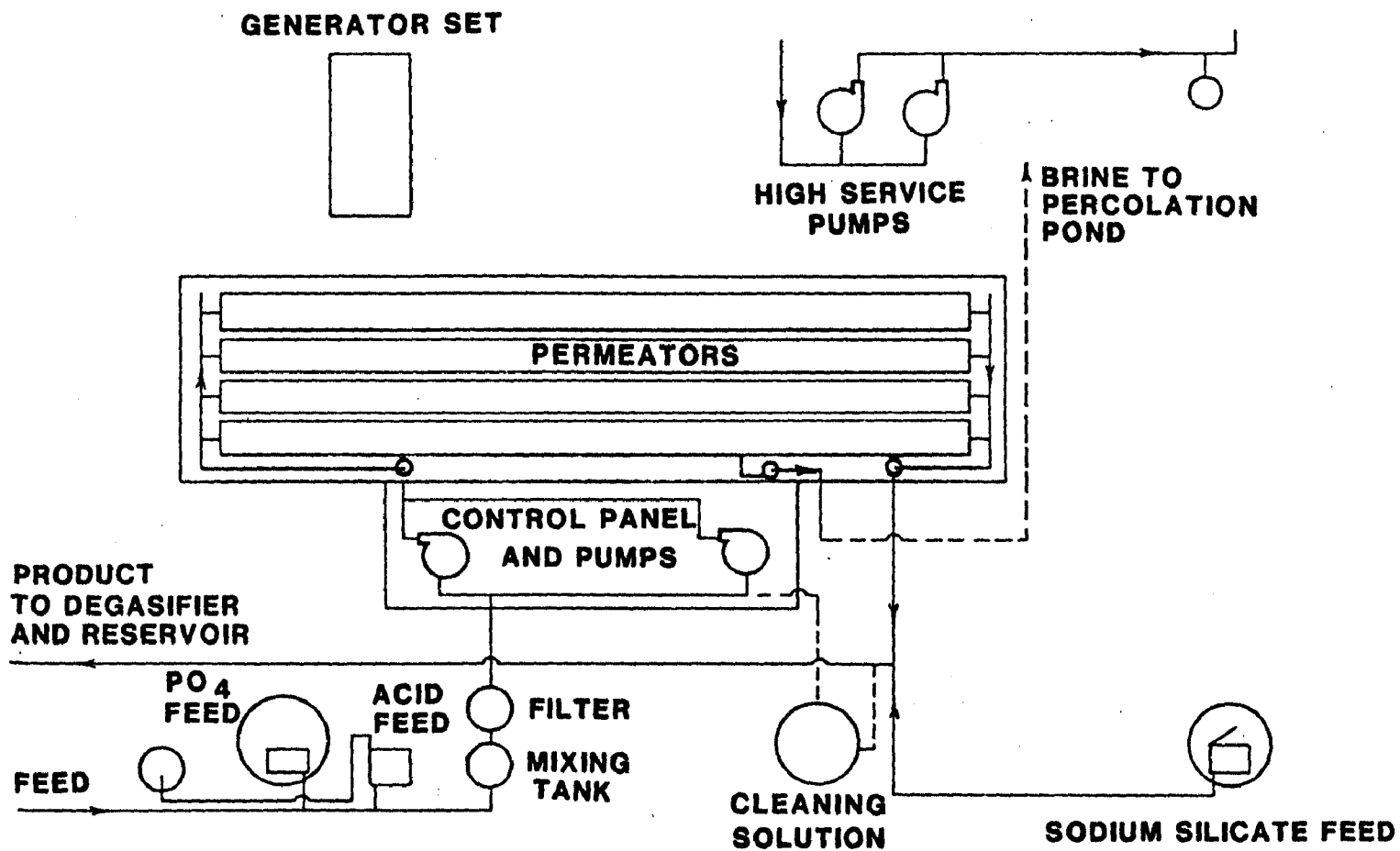
- Filter cartridge replacement
- Labor

5. Summary

   a. Advantages:

      - High removal of radium
      - High removal of other cations & anions
      - Small space requirement

   b. Disadvantages:

      - High operating costs
      - High capital costs
      - Disposal of reject waters

   c. Process Comparisons:

      - Reverse Osmosis: 96 percent removal
      - Lime Softening: 75 - 96 percent removal
      - Ion Exchange: 81 - 97 percent removal

II. ION EXCHANGE

Scope: Provide a review of the use of ion exchange technology for removing
inorganics from drinking water supplies, including design
considerations and limitations. Provide a case study of an
operating ion exchange facility, highlighting the design
considerations and costs.

A.   Design Considerations

1.   Process used to remove hardness and nitrate from groundwaters.
Inorganic removal occurs by absorption to resin exchange sites.

2.   Typical unit processes include:
- prefiltration
- ion exchange
- disinfection
- storage and distribution

3.   Process design considerations
- influent suspended solids
- competing ions (Ca & Mg)
- resin exchange capability
- resin break through times

4.   This process is generally effective for the treatment of the
following inorganic species:

Good to Excellent for:

Cationic	Anionic
Ba	As(V)
Cd	Cr(VI)
Cr(III)	Nitrate
Ag	Se(IV)
	Se(VI)

5.   Limitations - the process is effective for removing Ba and Ra
as well as other cations using cationic resins while anionic
resins are effective for nitrate and selenium.

B.   Case Study - McFarland, California

1.   Background Information

a.   System Characteristics
1)   Ground water supply
2)   4 wells (No.'s 1,2,3 and 4)
3)   All wells affected by nitrate
4)   Well No. 3 abandoned

       5)   Wells No.'s 1 and 4 used for current water supply, composite sample below 10 mg/L nitrate.
       6)   Well No. 2 treated

  b.   Water Quality (Raw)
     1)   Nitrate: 6.8 to 22.1 mg/L as N

2.   Plant Description
  a.   Plant Capacity: 695 gpm (1 MGD)
  b.   Current Finished Water Flow
     - Treated water: 500 gpm (71% of total)
     - Blend water: 200 gpm (29% of total)
  c.   Waste water
     - Saturated brine rate: 36 gpm
     - Diluted brine rate: 190.5 gpm
  d.   Treatment Processes
     - Anion exchange resin
     - Sodium chloride regeneration with slow rinse and resin declassification
     - Aerated lagoons and spray irrigation for brine waste treatment
     - Process schematic presented on Figure II-1

3.   Treatment Design
  a.   Nitrate level (basis for design)
     - Raw water: 16 mg/L (average)
     - Treated flow: 2.6 mg/L (average)
     - Finished flow (blend): 7.0 mg/L (average)
                      10.0 mg/L (maximum)
  b.   Media
     - Anion exchange resin (A-101-D, Duolite, Rohm and Haus Company, Philadelphia, PA.)
  c.   Bed Characteristics and Target Flows
     - Reaction vessels: 3, each 6 ft. diameter by 10 ft. high.
     - Bed depth: 3 feet (operating); 5 feet (maximum)
     - Treatment flow rate: 250 gpm
     - Empty Bed Contact Time: 2.54 minutes
     - Service loading rate: 9.03 gpm/ft^2

4.   Regeneration
  a.   Regeneration material
     - 6% sodium chloride brine (2.6 lbs/gal or 259 g/L)
  b.   Regeneration procedure
     - Saturated brine rate: 12.0 gpm
     - Diluted brine rate: 63.5 gpm
     - Brine rinse duration: 15 minutes
     - Bed volume treated per regeneration: 250
     - Downflow regeneration flow direction
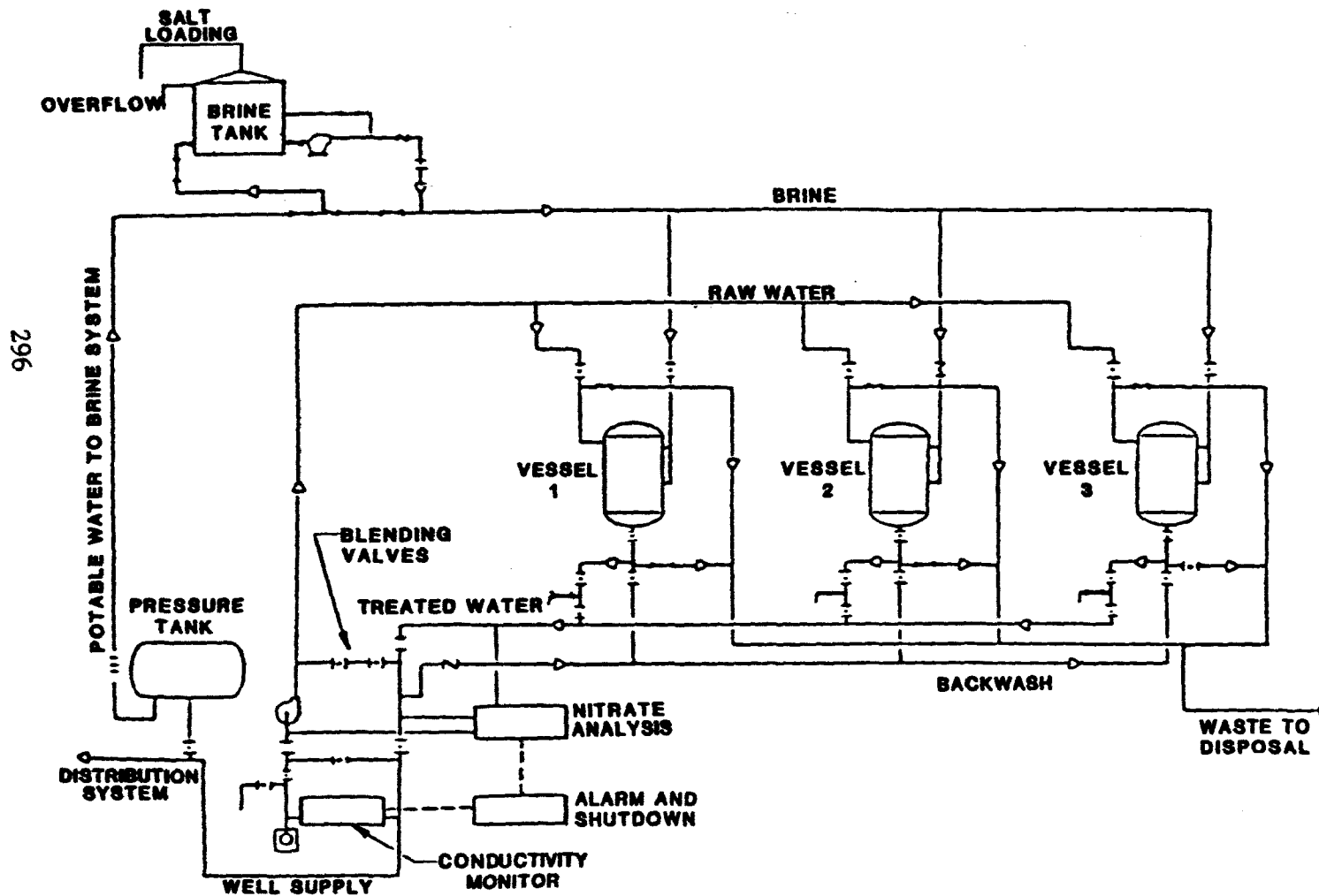
McFARLAND, CA.
TREATMENT PLANT FLOW DIAGRAM

FIGURE II-1

c. Slow Rinse procedure
- Slow rinse rate: 64 gpm
- Slow rinse duration: 30 to 50 minutes
- Downflow slow rinse flow direction

d. Resin declassification procedure
- Declassification flow rate: 140 gpm
- Declassification service rate: 5 gpm/ft^2
- Upflow declassification flow direction

5. Waste Handling
- Brine discharge to municipal wastewater treatment plant
- Brine treated by aerated lagoons with spray irrigation for animal feed crops and cotton.

6. Operations Data
a. Staggered reaction vessel operation; two operating and one regenerating at any given time.

b. Vessel regeneration
- Every 159,000 gallons per vessel at current operating conditions
- 1.47 times per day at current operating conditions
- 5.55 milliequivalents of chlorine per milliequivalent of nitrate removed
- 2162 lbs. salt required per day at continuous operation.

c. Plant performance
- Toleration of some nitrate leakage in treated water (2-5 mg/L)
- Finished water nitrate range: 6.2 to 8.3 mg NO_3-N/L
- Finished water chloride concentration: 166 mg/L
- 270.7 milliequivalents of nitrate removed per liter of resin
- Average nitrate removal before breakthrough: 14.33 mg/L
- Resin replacement 20% per year

d. Plant operations
- Microprocessor control with flow, product water nitrate and product water conductivity sensors
- At full automation once a day plant monitoring required

7. Costs
a. Construction (1983): $354,638   which includes:
- Ion Exchange vessels: 111,741
- Brine tank   18,700
- On-site construction   81,154
- Other   40,045
- Resin   56,610
- Engineering   46,388

b. Operating and Maintenance Costs: 12.8¢ per 1000 gallons which includes:
- Operator: 1.3¢ per 1000 gallons
- Power: 2.2¢ per 1000 gallons

297

- Resin replacement: 3.2¢ per 1000 gallons
- Salt: 3.4¢ per 1000 gallons
- Normal O & M: 1.9¢ per 1000 gallons
- Miscellaneous   0.8¢ per 1000 gallons

III. ACTIVATED ALUMINA

Scope: Provide a review of the use of ion exchange technology for removing inorganics from drinking water supplies, including design considerations and limitations. Provide a case study of an operating ion exchange facility, highlighting the design considerations and costs.

A. Design Considerations

1. Process used to remove fluoride from groundwaters. Inorganic chemical removal occurs through absorption on the activated alumina. A process schematic is presented as Figure III-1.

2. Typical unit processes include:
   - raw water pumpage
   - pretreatment
   - activated alumina contact
   - disinfection
   - storage and distribution

3. Process design considerations
   - influent suspend solids (pretreatment)
   - competing ions
   - alumina exchange ability

4. This process is generally effective for the treatment of the following inorganic species:

   Good to Excellent for:

   As(V)
   F
   Se(IV)

5. Limitations - the process is effective in removing fluoride, arsenic and selenium. The system is not effective in removing Ba, Ra, or Cd.

B. Case Study - Gila Bend, Arizona

1. Background Information
   a. System Characteristics
      - ground water supply
      - 3 wells (Nos. 1, 2 and 4)
      - chlorination of selected wells
      - wells affected by high fluorides
      - Well No. 4 treated

ACTIVATED ALUMINA

300

RAW WATER → [PRETREATMENT] → [ACTIVATED ALUMINA ION EXCHANGE] → DISINFECTION →

FIGURE III-1
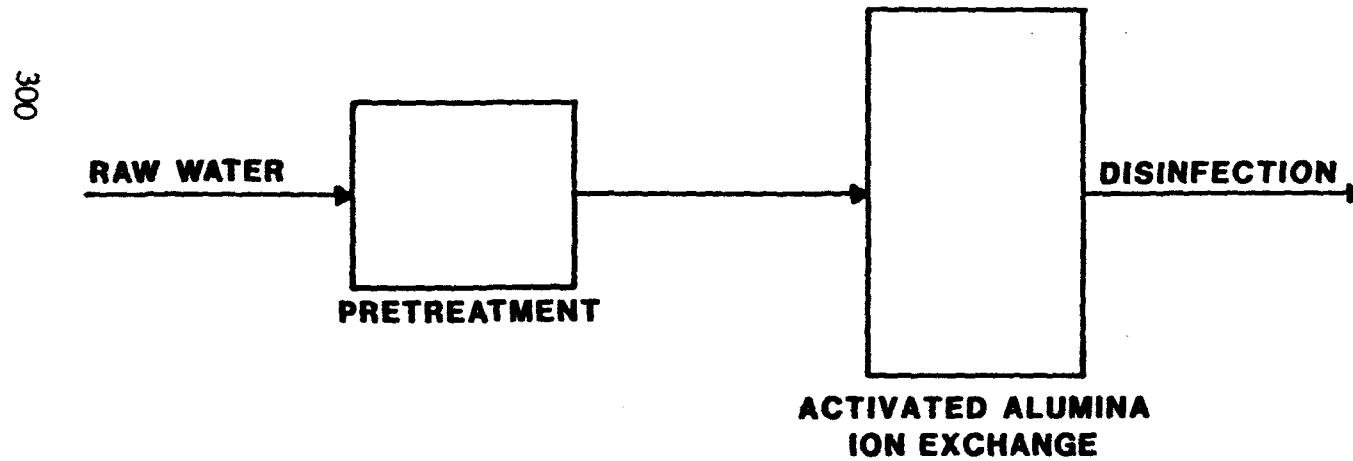
b. Water Quality
   - Fluoride: 4 to 6 mg/L
2. Plant Description
   a. Plant Capacity: 600 gpm (900 gpm max.)
   b. Treated water total flow - 90 percent raw water flow - 750,000 gpd
   c. Waste water - 10 percent raw water flow - 75,000 gpd
   d. Treatment Processes
      - activated alumina
      - caustic regeneration
      - acid neutralization
      - evaporation pond for regenerant waste treatment
      - flow schematics presented in Figure III-2
3. Treatment Design
   a. Fluoride levels (basis for design)
      - Raw Water - 5.0 ppm (ave.)
      - Treated Water - 0.7 ppm (ave.)
                        1.4 ppm (max.)
   b. Media
      - Material Spec. - Alcoa Activated Alumina - Grade F-1, -28 + 48 mesh

      - Bed material capability to remove fluoride - 1,000 grains/ft^3

      - Desert Center, California - 1,000 + grains/ft^3 with 7.5 ppm fluoride

      - Alcoa Laboratory - 700 grains/ft^3 with 22 ppm fluoride

      - X9 Ranch - 1,000 + grains/ft^3 with 4 ppm fluoride.

   c. Bed Design

      - Number of treatment units - 2, each 10 ft diameter by 10 ft high

      - Bed depth - 5 feet - 0 inches

      - Bed expansion during backwash - 50 percent = 2 feet - 6 inches

      - Tank free board - 6 inches

      - Superficial residence time of raw water flowing through bed - 5 minutes (min.)

      - Treatment unit flow rate - 7 gpm/ft^2 (max)

      - Treatment unit backwash flow rate - 11 gpm/ft^2 (max)

301

BASIC OPERATING MODE FLOW SCHEMATICS

RAW WATER

ACID

TREATED WATER

TREATMENT UNIT

TREATMENT AND DOWNFLOW RINSE

RAW WATER

TREATMENT UNIT

WASTE

BACKWASH AND UPFLOW RINSE

RAW WATER

CAUSTIC

TREATMENT UNIT

WASTE

UPFLOW REGENERATION

RAW WATER

CAUSTIC

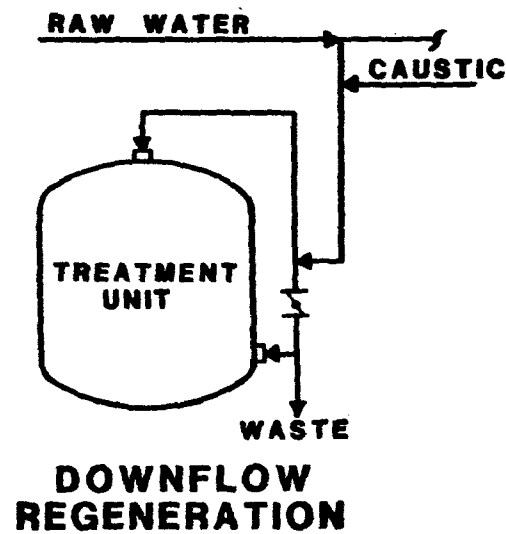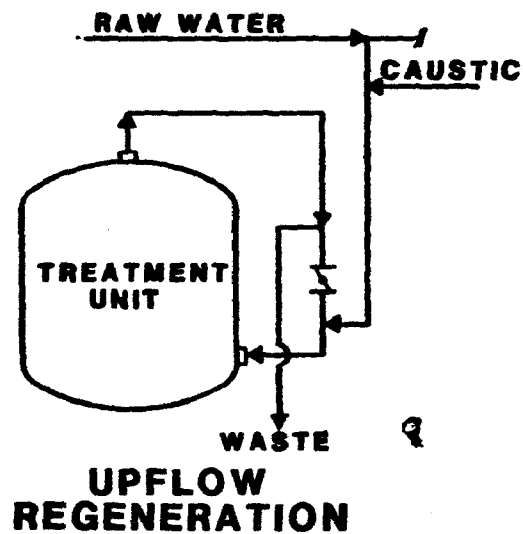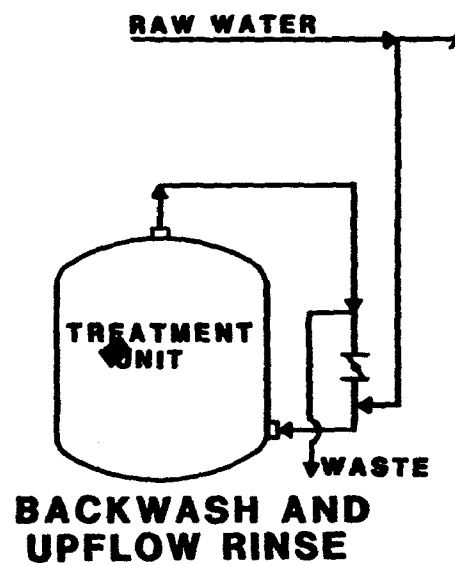TREATMENT UNIT

WASTE

DOWNFLOW REGENERATION
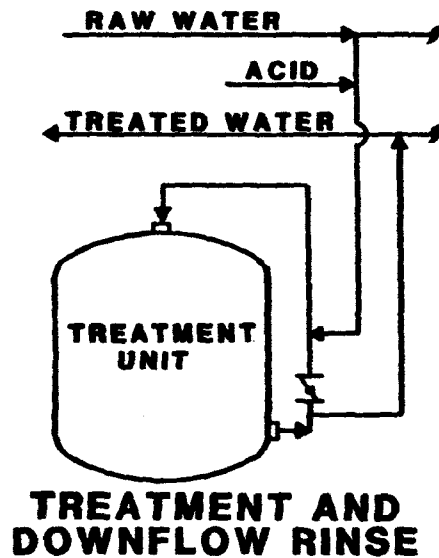
FIGURE III-2

4. Regeneration and Neutralization
   a. Regeneration material - 1 percent NaOH

      - Blend of 50 percent NaOH and raw water in "mixing T" at treatment unit

      - Fifty percent NaOH procured directly from caustic manufacturer, delivered to plant in tank trucks

   b. Regeneration process

      - Flow rate through treatment unit - 2-1/2 gpm/ft^2 (max)

      - Residence time in treatment bed - 24 minutes (min.)

      - Amount of caustic required/regeneration - 200 gallons/lb fluoride in bed

      - Incorporate provision for upflow or downflow through bed

   c. Neutralization material - 0.04 percent H_2SO_4

      - Blend of 93 percent H_2SO_4 and raw water in "mixing T" at treatment unit

      - Ninety-three percent H_2SO_4 procured directly from acid manufacturer, delivered to plant in tank trucks

   d. Neutralization process

      - Flow rate through treatment unit - 7 gpm/ft^2 (max.)

      - Amount of acid rinse required - sufficient to adjust pH within acceptable pH limits 6.5 - 8.5

      - Incorporate provision for upflow or downflow through bed

5. Waste Handling
   a. Nontoxic wastes (backwash, neutral rinse water) discharged to sewer
   b. Regenerant waste discharge to lined evaporation pond (240 ft by 440 ft by 9 ft deep)

6. Operating Data
   a. Regenerate every 3.5 to 4 mg of water treated
   b. Ten hours to regenerate

c.   Activated alumina media lost: 10-12 percent per year
d.   Water temperature: 107 F
e.   Operating data presented in Figure III-3

7.   Costs
  a.   Construction (1977-78): $285,000 which includes:
       - treatment facility
       - well
       - 0.5 mg steel tank
       - pond
       - booster pumps and standby generator
       - chlorine facilities
  b.   Operating costs: 27 to 28¢ per 1,000 gallons
       - salary
       - power
       - chemicals
       - media replacement

TYPICAL OPERATING RUN
AT GILA BEND, AZ.
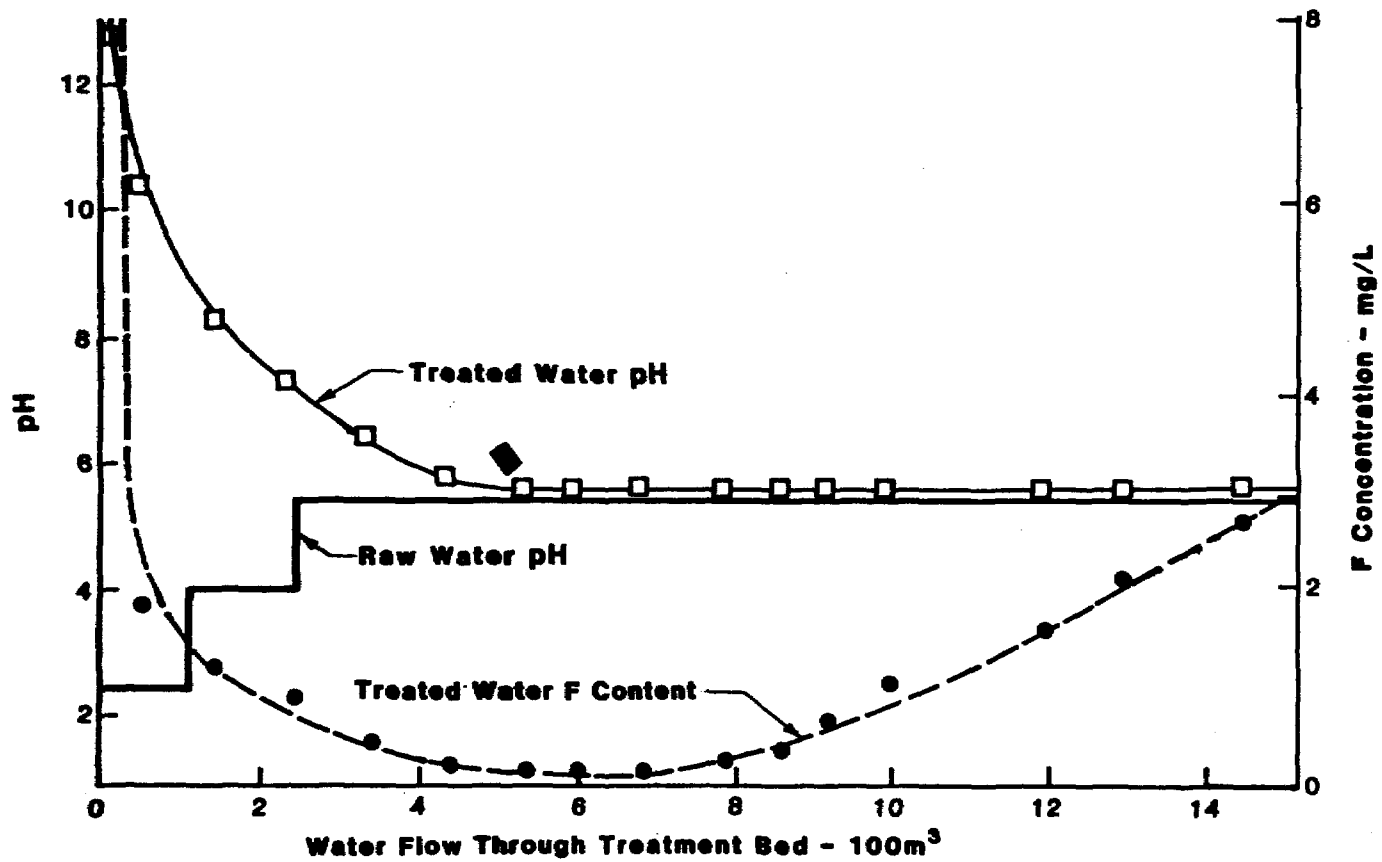
FIGURE III-3

IV. PROCESS SELECTION

Scope: Review the various factors that must be considered when selecting a treatment process for removing inorganics from drinking water supplies.

1. Historical IOC concentration

   a. Dependency on raw water concentration level since most technologies rely on a percent removal basis.

   b. Valence state of the metal very important to the design strategy.

   c. Type and concentration of the asbestos fiber present critical to effective design.

2. Process residues or waste products Disposal of wastes need special consideration since the residuals are often considered hazardous wastes and may be regulated under CERCLA.

   a. Conventional processes produce sludges
   b. Lime softening processes produce sludges
   c. Ion exchange produces brines
   d. Reverse Osmosis produces brines
   e. Activated Alumina produces brines

3. Existing Process may be modified using one of the above technologies.

4. Pretreatment Requirements

   a. Surface waters require filtration prior to membrane or ion exchange processes.

   b. Stability requirements

   c. Ground water systems may have little in existing conventional treatment-generally leaving choices more open.

5. Flow versus Type of Treatment

   a. Size of plant determines the feasible treatment method (economy of scale)

   b. Process selection depends on not only flow but the presence of other, undesired contaminants such as Secondary Drinking Water parameters.

6. Other Considerations

    a. Availability of local supply of process chemicals
    b. Power costs

MOST PROBABLE APPLICATION

PROCESS	REMOVES	FROM
CONVENTIONAL	Cd, Cr. As, Ag, Pb	SURFACE WATER
LIME SOFTENING	Ba, Cd, Cr, (III), F, As, V, Pb	GROUNDWATER, HARD SURFACE WATER
CATION EXCHANGE	Ba	GROUNDWATER
ANION EXCHANGE	NO_3	GROUNDWATER
ACTIVATED ALUMINA	F, As, Se	GROUNDWATER
POWERED ACTIVATED CARBON	Hg	SURFACE WATER (SPILLS)
GRANULAR ACTIVATED CARBON	Hg	SURFACE OR GROUNDWATER
REVERSE OSMOSIS AND ELECTRODIALYSIS	ALL INORGANICS	GROUNDWATER

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6. Rubel, F. Jr.; and Woolsey, R. D. "The Removal of Excess Fluoride from Drinking Water by Activated Alumina." Journal AWWA, 71:1:45 (January 1979).

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8. Sorg, T. J.; and Logsdon, G. S. "Treatment Technology to Meet the Interim Primary Drinking Water Regulations for Inorganics: Part 2." Journal AWWA, 70:7:379 (July 1978).

9. Sorg, T. J.; Csanady, M.; and Logsdon, G. S. "Treatment Technology to Meet the Interim Primary Drinking Water Regulations for Inorganics: Part 3." Journal AWWA, 70:12:680 (December 1978).

10. Sorg, T. J. "Treatment Technology to Meet the Interim Primary Drinking Water Regulations For Organics: Part 4." Journal AWWA, 71:8:454 (August 1979).

11. Sorg, T. J.; and Longdon, G. S. "Treatment Technology to Meet the Interim Primary Drinking Water Regulations for Inorganics: Part 5." Journal AWWA, 72:7:411 (July 1980).

12. V. J. Ciccone and Associates, Inc. "Technologies and Costs for the Removal of * from Potable Water Supplies." Science and Technology Branch, Criteria and Standards Division, Office of Drinking Water, U. S. Environmental Protection Agency, Washington, D. C.

*Arsenic
 Asbestos
 Barium
 Cadmium
 Chromium
 Cyanide
 Lead
 Mercury
 Molybdenum
 Nickel
 Nitrates and Nitrites
 Selenium
 Silver
 Sodium
 Sulfates

C.

ORGANICS TREATMENT

OVERVIEW AND CASE STUDIES

I. GRANULAR ACTIVATED CARBON - TREATMENT OVERVIEW

II. GRANULAR ACTIVATED CARBON - CASE STUDIES

III. AERATION - TREATMENT OVERVIEW

IV. AERATION - CASE STUDY

I. GRANULAR ACTIVATED CARBON - TREATMENT OVERVIEW

Scope: Present a review of the use of granular activated carbon adsorption technology for removing organics from drinking water supplies, including adsorption principles, process design considerations, facility design considerations, and costs.

A. PRINCIPLES OF ADSORPTION

1. Adsorption - the transfer of a dissolved contaminant (adsorbate) from a solvent (solution) to the surface of an adsorbent (carbon). See Figure I-1 for schematic of an adsorption system.

2. Attractive Adsorption Forces

   - physical: Van der Waals forces
   - chemical
   - electrical

3. Factors Affecting Adsorption Process

   a. Adsorbate - see Tables I-1 and I-2 for lists of readily adsorbed and poorly adsorbed organics, respectively.

      - branched-chain compounds more adsorbable than straight-chained compounds

      - increasing molecular weight increases adsorption

      - lower solubility increases adsorption.

      - greater concentration, increased adsorbability

   b. Adsorbent

      - high degree of porosity
      - extensive internal surface area
      - affinity of adsorbate for absorbent (polar, nonpolar)

   c. Aqueous Solution

      - temperature
      - pH
      - dissolved solids
      - other adsorbates

4. Forms of Activated Carbon

   a. Granular
   b. Powdered

FIGURE I-1

Solvent

Adsorbate

Adsorbent

Attached
Adsorbate
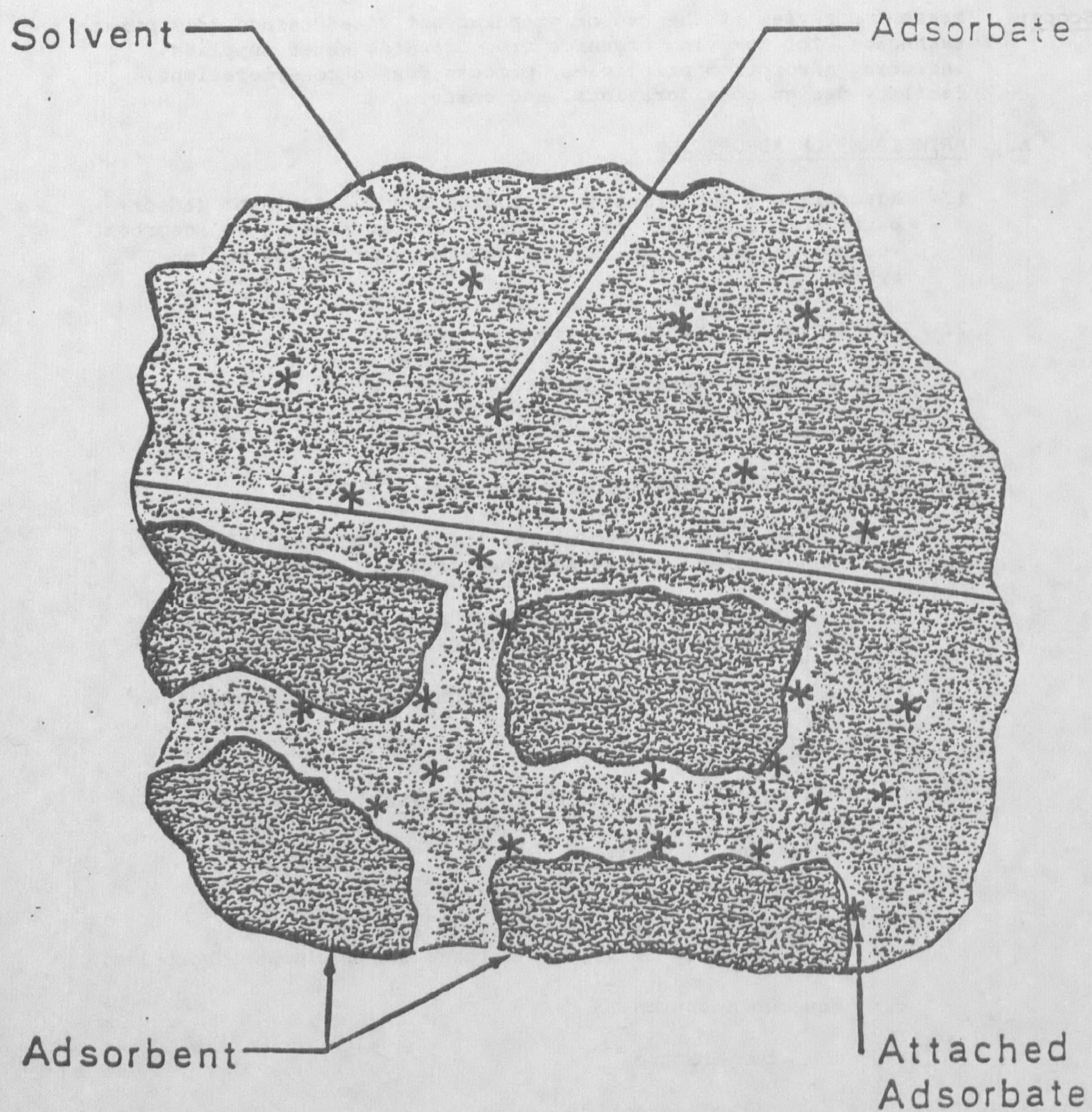
THE ADSORPTION SYSTEM

TABLE I-1

READILY ADSORBED ORGANICS

- Aromatic Solvents

    Benzene, toluene, nitrobenzenes

- Chlorinated Aromatics

    PCBs, chlorobenzenes, chloronapthalene

- Phenol and chlorophenols

- Polynuclear Aromatics

    Acenapthene, benzopyrenes

- Pesticides and herbicides

    DDT, aldrin, chlordane, heptachlor

- Chlorinated non-aromatics

    Carbon tetrachloride, chloroalkyl ethers

- High MW Hydrocarbons

    Dyes, gasoline, amines, humics

TABLE I-2

POORLY ADSORBED ORGANICS

- Alcohols
- Low MW Ketones, Acids, and Aldehydes
- Sugars and Starches
- Very High MW or Colloidal Organics
- Low MW Aliphatics

314

B.   GAC PROCESS DESIGN CONSIDERATIONS

    1.   GAC process design considerations:

        a.   contaminant

        b.   levels

        c.   GAC

        d.   carbon usage rate – pounds of carbon per gallon of water
            treated

        e.   empty bed contact time (5-30 minutes)

        f.   surface loading rate (2 to 10 gpm/sf)

        g.   carbon depth (10-30 ft)

    2.   Empty Bed Contact Time

        a.   Affects capital costs
        b.   5 to 30 minutes
        c.   Average – 10 minutes for most organics
        d.   Radon – 100 to 200 minutes

    3.   Carbon Usage Rate

        a.   Rate of carbon adsorption
        b.   Affects O&M cost
        c.   100 to 300 lb/mg for most organics

    4.   Carbon Usage Rates for Several Organics:

        a.   Volatile Organics

	lb/MG
TCE –	200
PCE –	70
Vinyl Chloride –	NA
Cis-1,2-Dichloroethylene –	250

        b.   Pesticides

Aldicarb –	25
Chlordane –	5
DBCP –	15

c. Chlorinated Aromatics

PCB -   5
Dichlorobenzene -   10

4. Carbon Adsorption Testing

   a. Isotherm (laboratory) - Figure I-2 indicates isotherms for several organic chemicals

   b. Freundlich Isotherm Relationship:

      $x/m = kc^{1/n}$
      x/m = equilibrium capacity (mg SOC/gm carbon)
      k = capacity at 1 mg/L SOC concentration
      c = SOC effluent concentration (mg/L)
      1/n = exponent

   c. Minicolumns (laboratory) see diagram on Figure I-3

   d. Dynamic columns (field)

5. Effects of Different Organics on GAC Designs

   a. Contaminant levels - see Figure I-4
   b. Type of Compound - see Figure I-5

C. GAC FACILITY DESIGN CONSIDERATIONS

   1. Major Process Elements

      a. Carbon contactors
      b. Transfer system
      c. Regeneration system

   2. Carbon Contactor Configuration

      a. Upflow

         - long contact times
         - suspended solids removal

      b. Downflow

         - Pressure - see diagram on Figure I-6
         - Gravity - see diagram on Figure I-7

316

FIGURE I-2
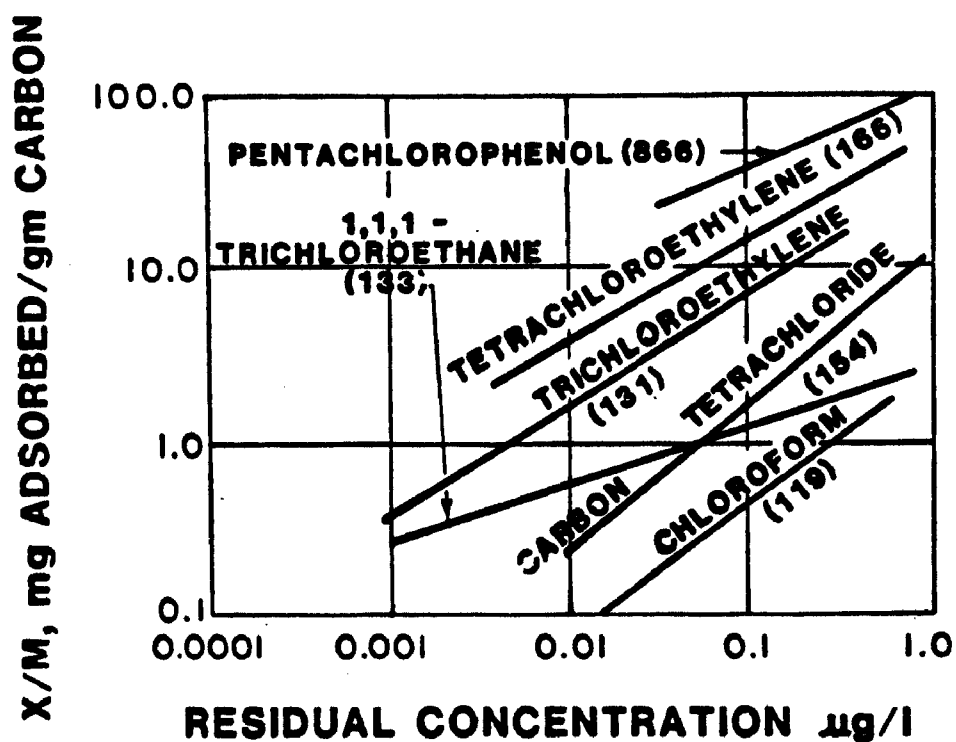
NOTE: NUMBER IN PARENTHESIS (166) INDICATES
THE MOLECULAR WEIGHT OF THE COMPOUND

ADSORPTION ISOTHERMS FOR SEVERAL ORGANIC
COMPOUNDS FOUND IN GROUND WATER SUPPLIES
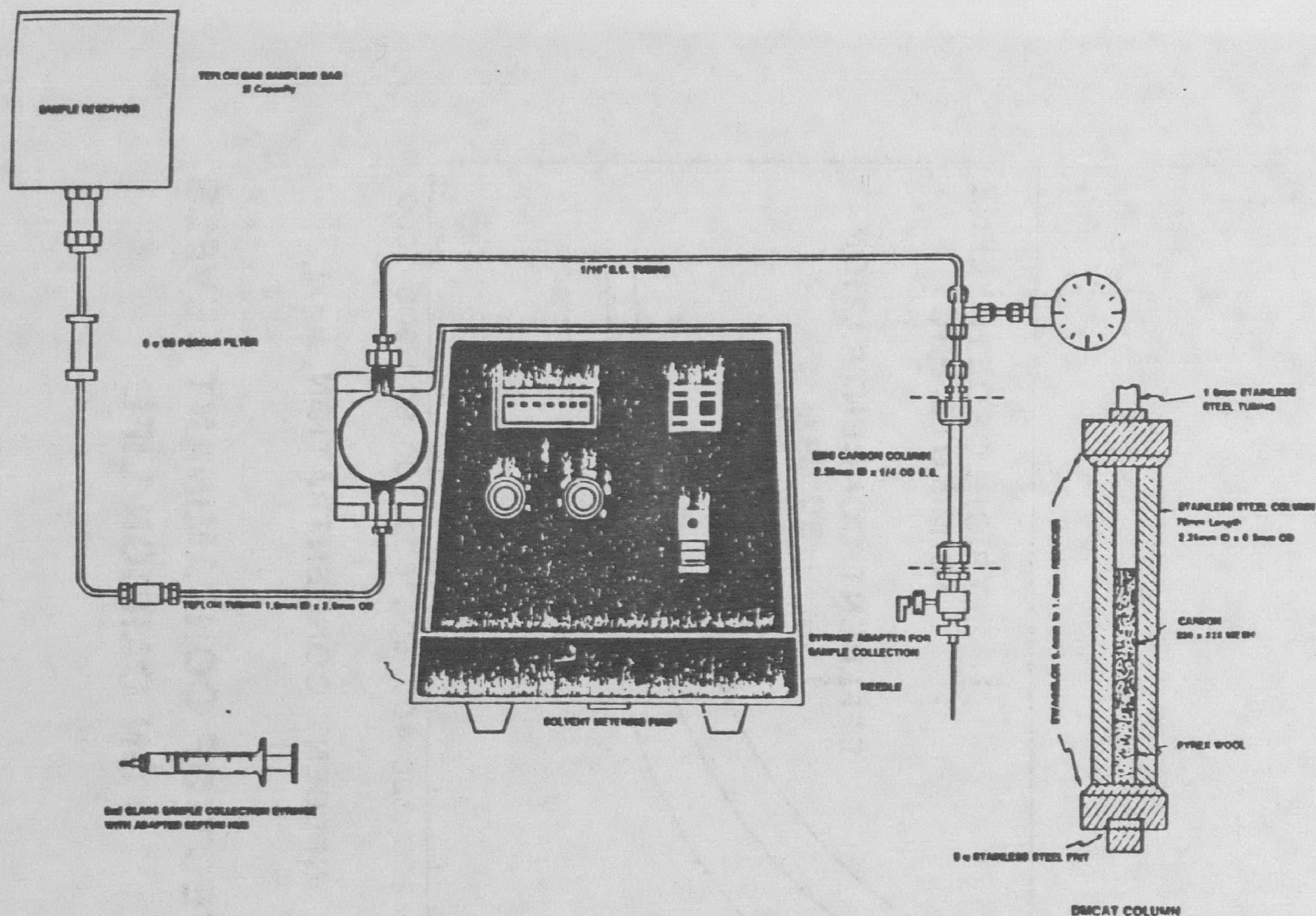
DIAGRAM OF DYNAMIC MINI-COLUMN ADSORPTION TECHNIQUE SYSTEM

FIGURE I-3

FIGURE I-4
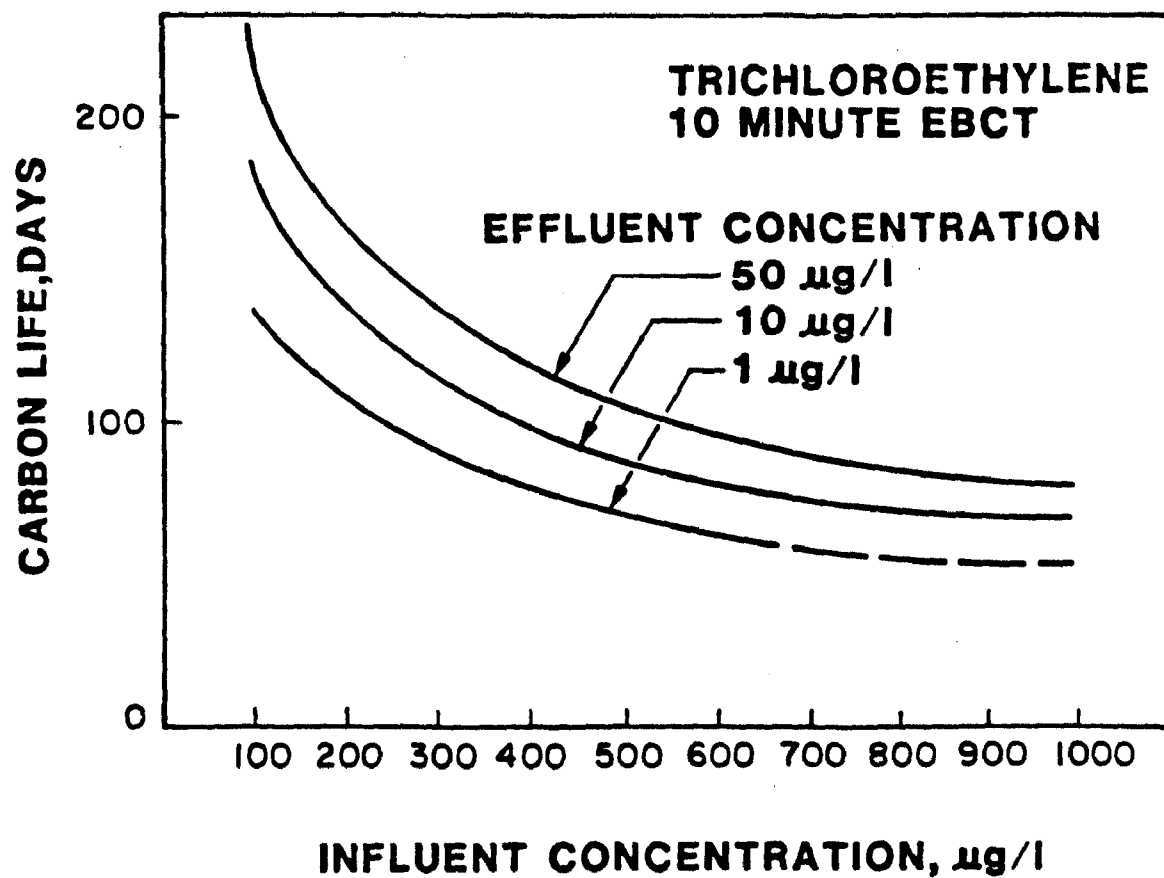
EFFECT OF CONTAMINANT LEVELS
ON CARBON LIFE

FIGURE I-5
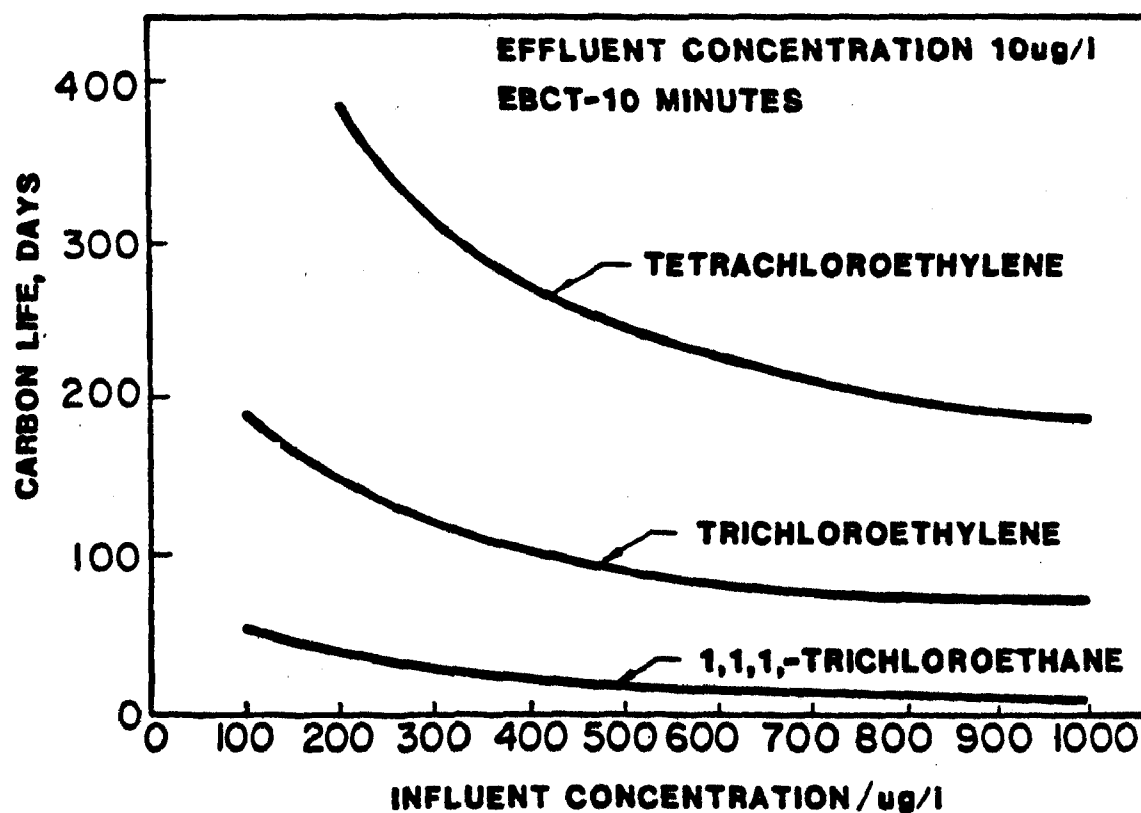
EFFECT OF TYPE OF COMPOUND ON CARBON LIFE

FIGURE I-6

INFLUENT →

90psi

20,000 LB EA.
GRANULAR
ACTIVATED CARBON →

COLLECTOR
SYSTEM

TO SYSTEM —

TREATED WATER
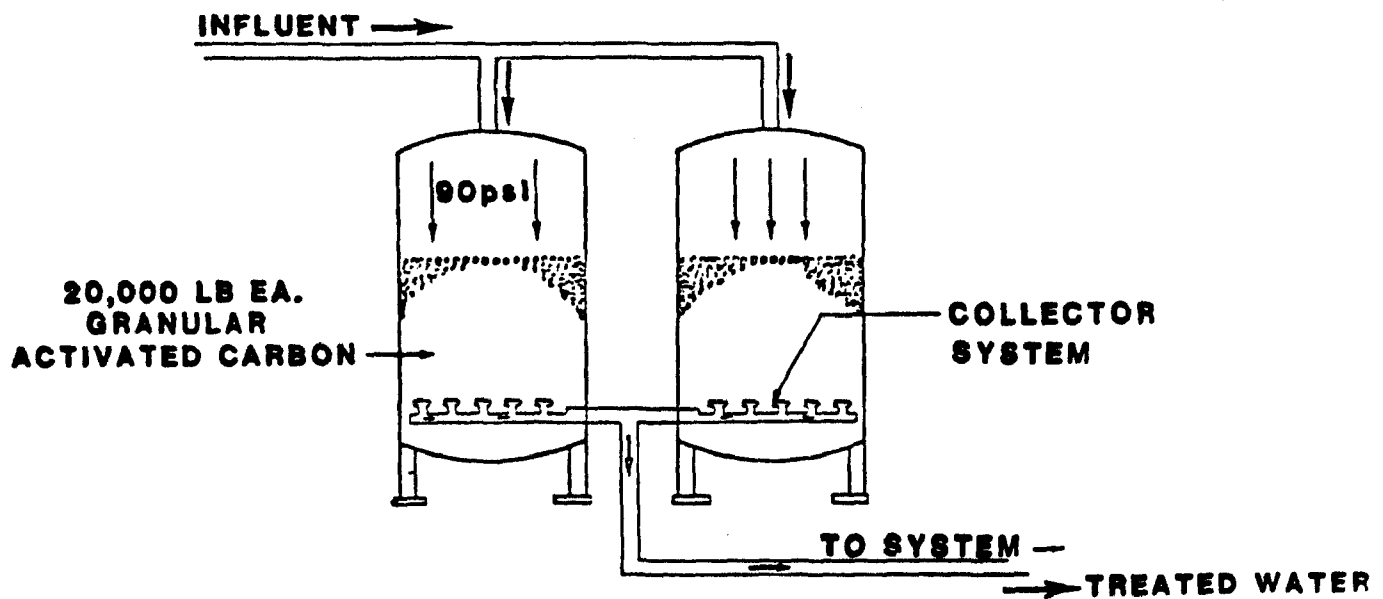
GAC CONTACTORS

SCHEMATIC OF TREATMENT PROCESSES

321

FIGURE 1-7
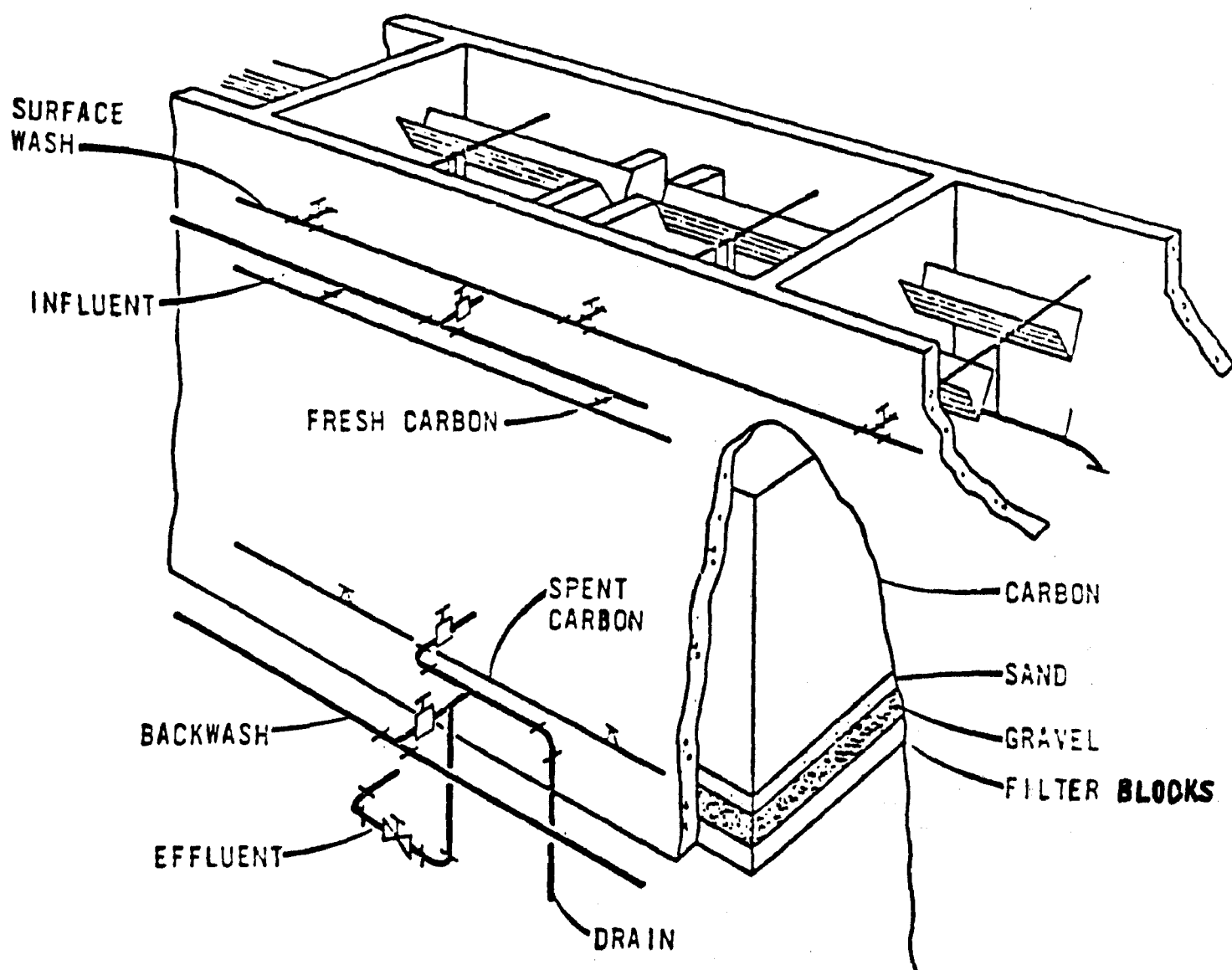
DOWNFLOW GRAVITY CONTACTOR

3. Transfer System

   a. Hydraulics
   b. Velocities
   c. Materials of construction
   d. GAC loss

4. GAC regeneration:

   a. On-Site Regeneration - economical where carbon exhaustion rate is greater than 2,000 pounds per day.

   b. Off-Site Regeneration - economical where carbon exhaustion rate falls between 500 and 2,000 pounds per day.

   c. Off-Site Disposal - economical where carbon exhaustion rate is less than 500 pounds per day.

5. Operational Issues

   a. Desorption

   b. Replacement

   c. Bacterial growth

   d. Mass transfer - defines breakthrough curve or wavefront (see Figure I-8)

6. Waste Disposal

   a. Backwash
   b. Spent carbon

D. GAC TREATMENT ECONOMICS

1. Capital cost components include:

Basic	Site Specific
contactors	special sitework
activated carbon	raw water holding tank
piping	new/restaged well pump
	GAC contactor building
	chemical facility
	clearwell
	finished water pump(s)
	backwash storage

2. Capital costs are shown on Figure I-9 at end of this section.

323
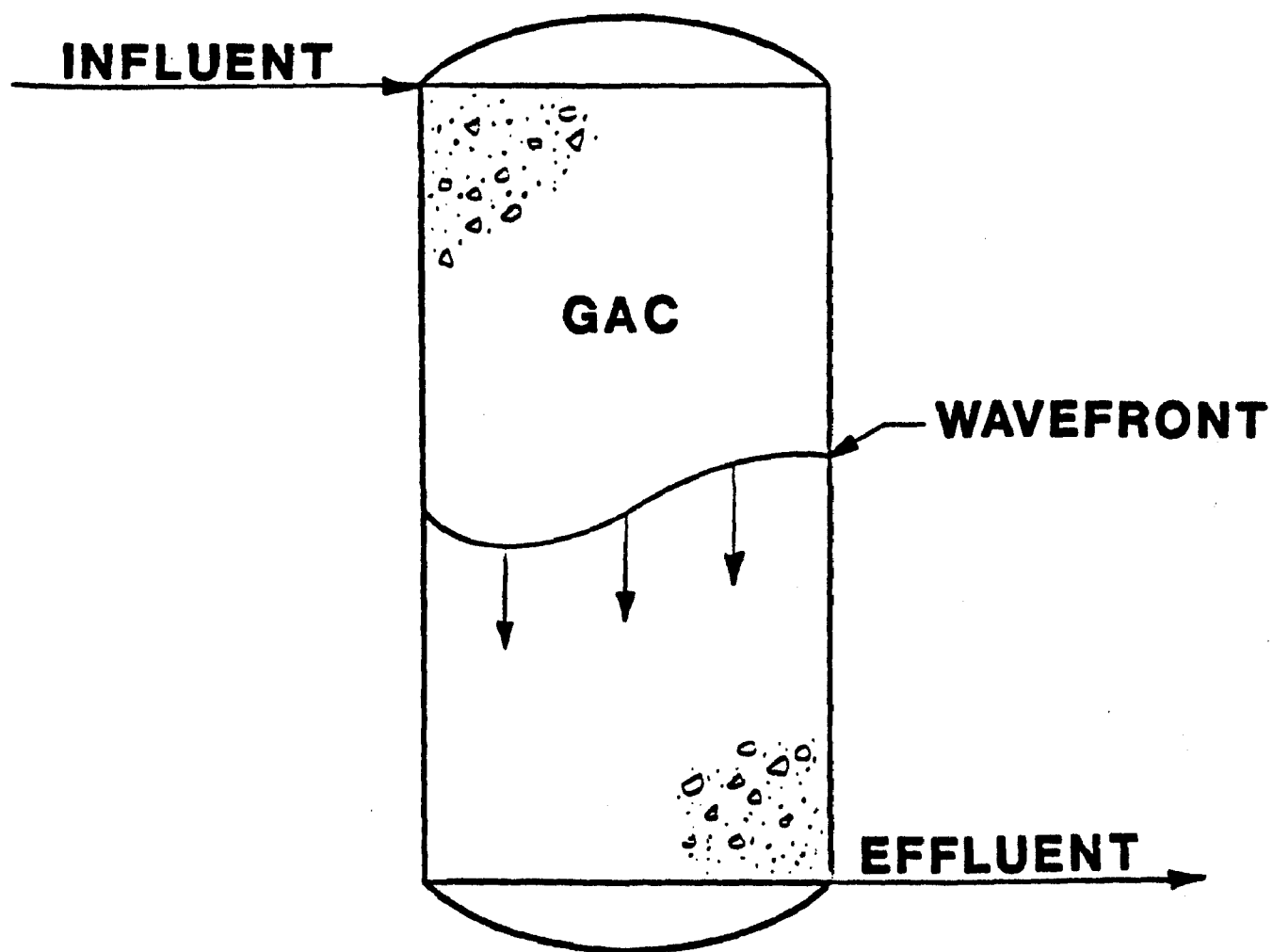
FIGURE I-8

GAC CONTACTOR

CAPITAL COSTS FOR GAC SYSTEMS
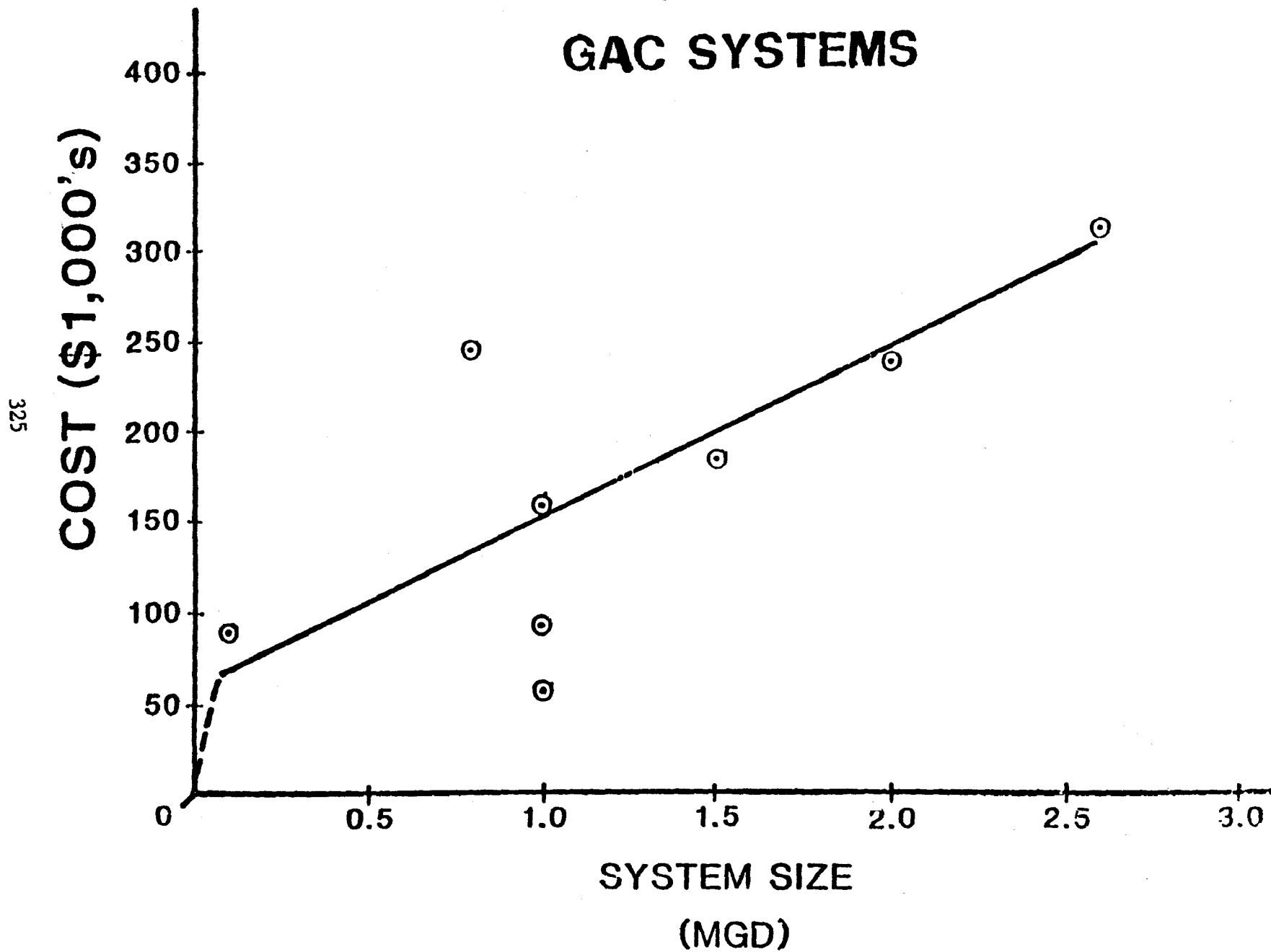
FIGURE I-9

3. Operating costs are shown on Figure I-10 at end of this section.

4. Relative costs for organics removal

Chlorinated aromatics -   least costly
Pesticides - $\downarrow$
VOCs -   most costly

O & M COSTS FOR GAC SYSTEM

FIGURE I-10
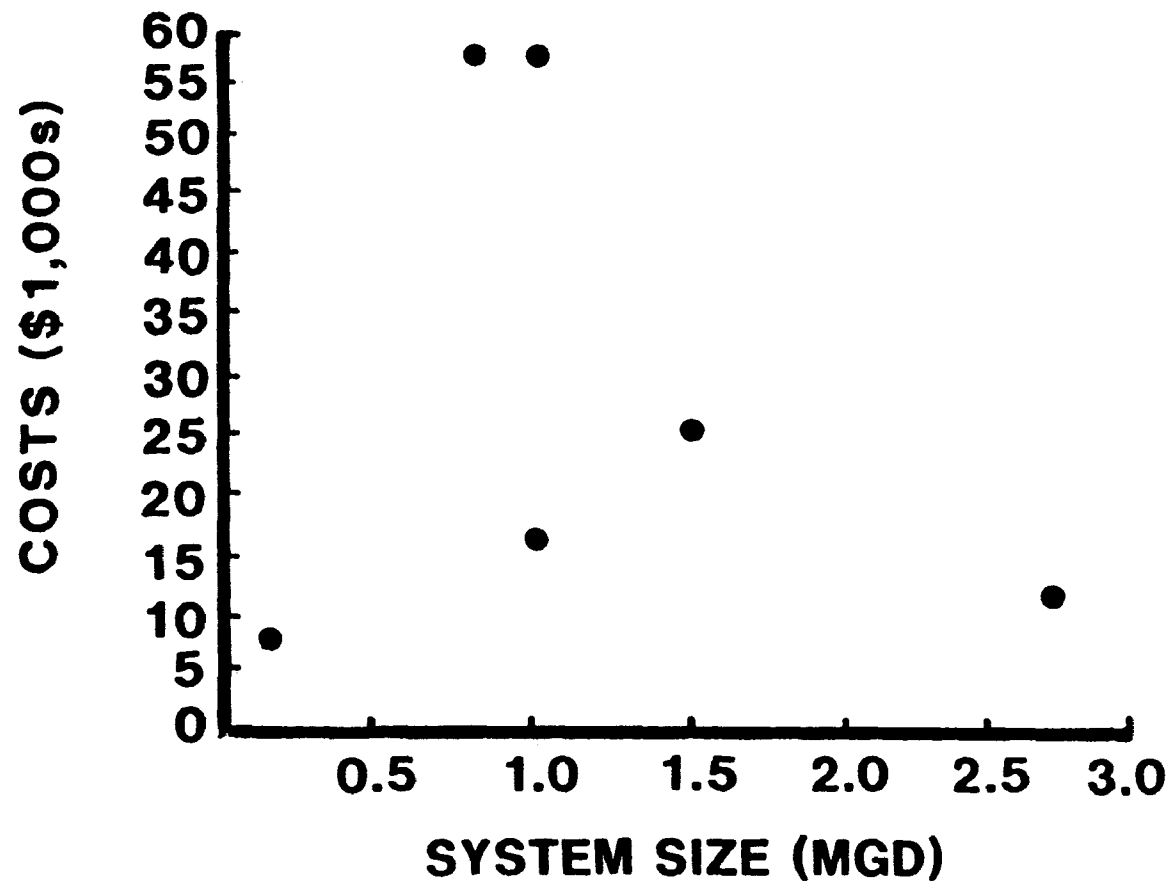
II. GRANULAR ACTIVATED CARBON - CASE STUDIES

Scope: Describe experiences of two water supplies in dealing with organics contamination, including the use of granular activated carbon to treat their supply.

A. GAC ADSORPTION - WASHINGTON, NEW JERSEY

1. System Characteristics

   a. ground water supply
   b. 1 well
   c. 550 gpm, 0.792 mgd

2. Water Quality

   a. PCE: 50-500 ug/L
   b. TCE: 1-10 ug/L
   c. 1,1,1-Trichloroethane: 1-20 ug/L
   d. Carbon Tetrachloride: 1-5 ug/L
   e. See Figure II-1 for plot of VOC influent variations

3. Alternatives Considered

   a. GAC (selected)
   b. Resin
   c. New source of supply

4. GAC Design

   a. No. of Contactors: 2

   b. Mode of Operation: Series or Parallel, downflow, pressure

   c. Diam (ft): 7

   d. Carbon depth: (ft) 10

   e. Hydraulic Loading; (gpm/ft^2) 7.1

   f. EBCT (min): 10.5

   g. Washwater: sand-filtered and recycled

   h. See Figure II-2 for schematic of Vannatta Street Station

CONCENTRATION OF CONTAMINANTS IN THE RAW WATER

FIGURE II-I
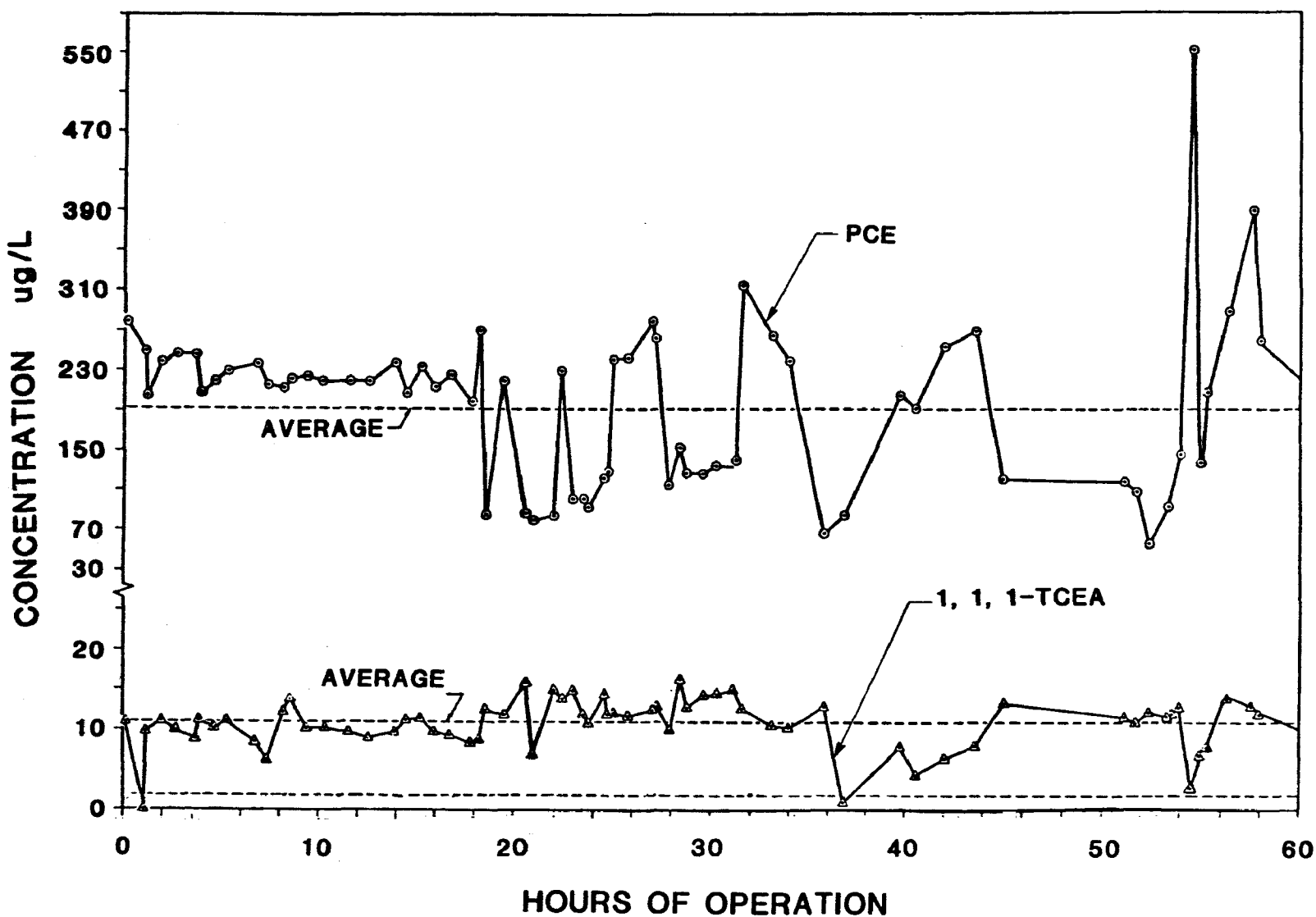
GAC TREATMENT PLANT SCHEMATIC
VANNATTA STREET STATION

CARBON

CARBON

CHLORINE

SAND

WASTEWATER RECYCLE

FILTERED WATER TO
DISTRIBUTION SYSTEM

330

FIGURE II-2
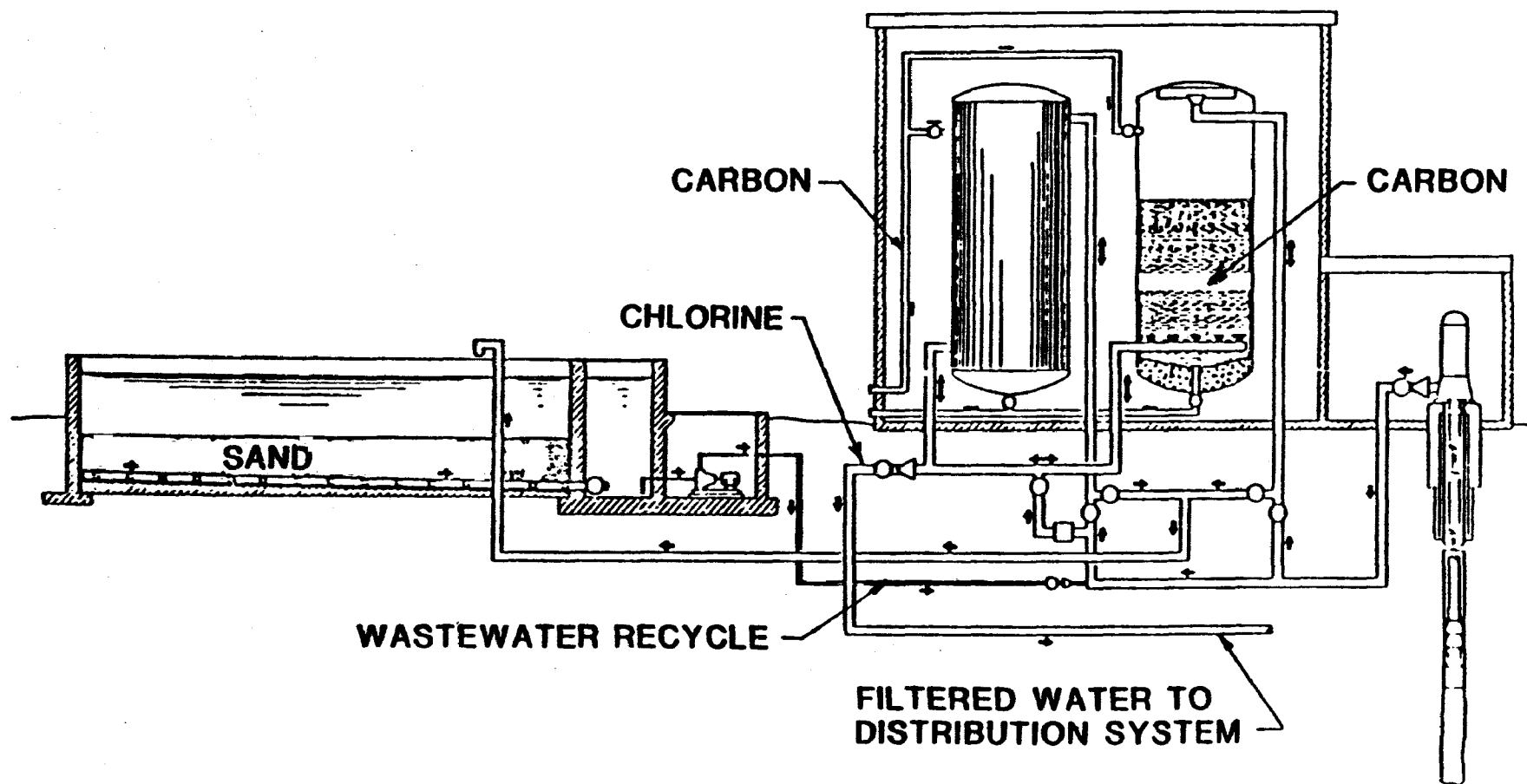
5. Carbon Usage Rates

<u>lbs GAC/mg</u>

PCE

Breakthrough	102
5 ug/L	91

1,1,1-TCEA

Breakthrough	271
10 ug/L	209

6. Costs

    a. Capital: $508,500 (1981)
    b. Operating: $80,000/year

B. <u>GAC ADSORPTION - CINCINNATI, OHIO</u>

1. System Characteristics

    a. supply: Ohio River

    b. capacity: 220 mgd

    c. existing treatment includes: high-rate pretreatment, presett-ling, conventional treatment (See Figure II-3)

2. Water Quality - see Figure II-4 for influent TOC variations

3. Cincinnati Project Goals

    a. Finished water TOC <1.0 mg/L
    b. Maximum use of existing WTP facilities
    c. Flexible system to accommodate future regulations
    d. System costs within reasonable limits

4. GAC Design Concepts

    a. Post-filtration adsorption using downflow deep-bed contactors.
    b. Post-GAC chlorination.
    c. On-site carbon regeneration utilizing fluidized bed furnaces.
    d. Minimization of carbon losses.

5. See Figure II-5 for schematic of Cincinnati treatment train

331

FIGURE II-3

CINCINNATI TREATMENT TRAIN
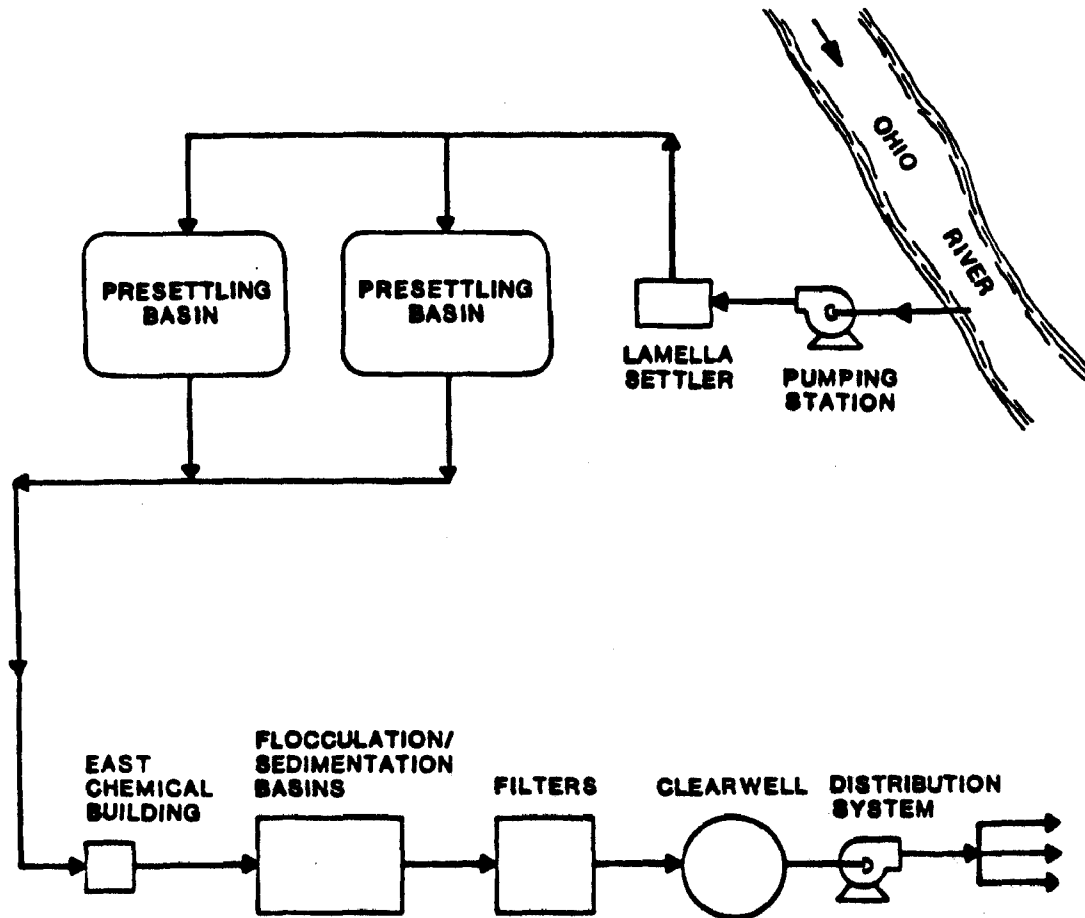
TYPICAL TOC REDUCTION CURVE DURING PILOT STUDY

FIGURE II-4

FIGURE II-5
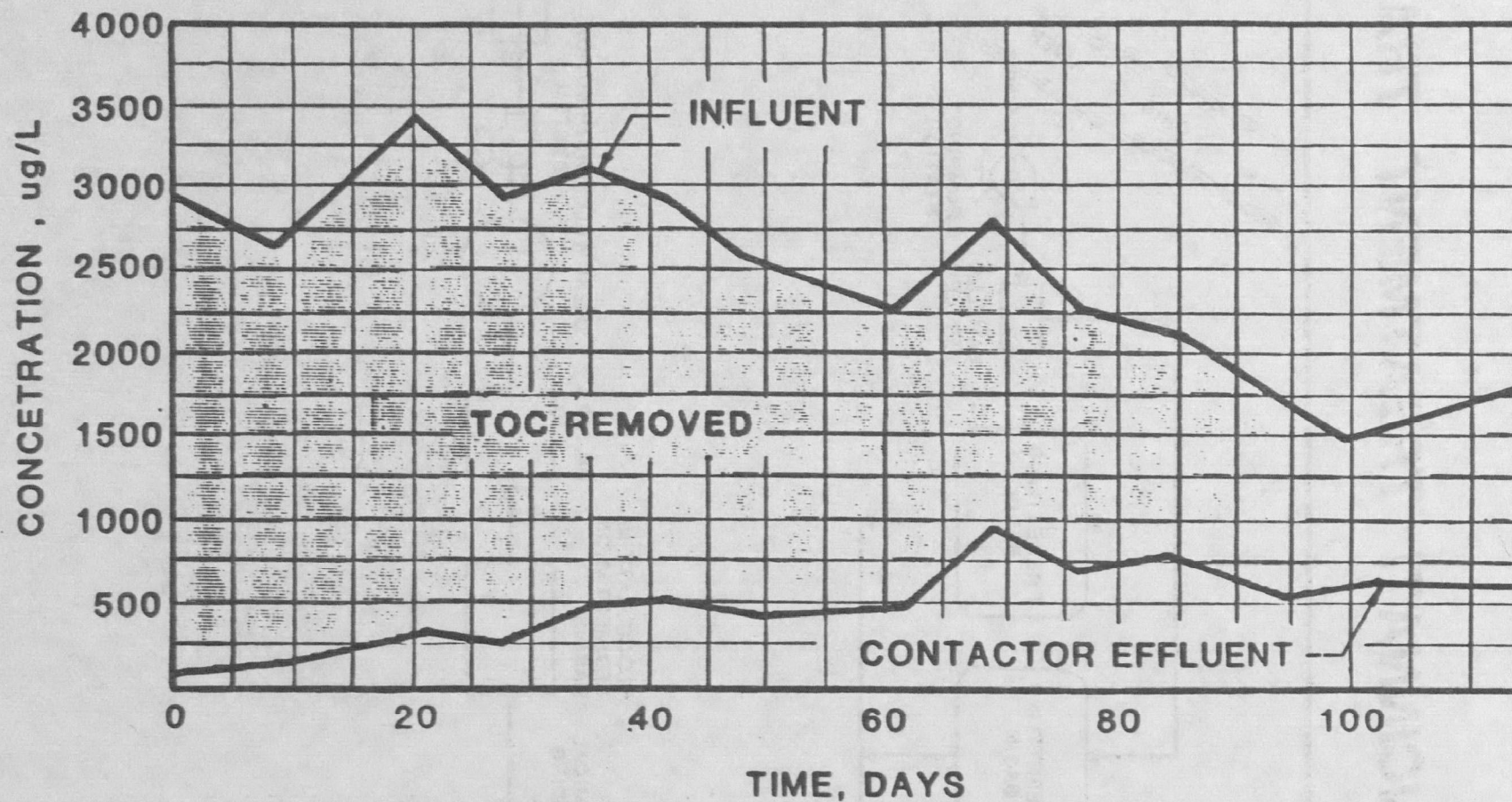
CINCINNATI TREATMENT TRAIN
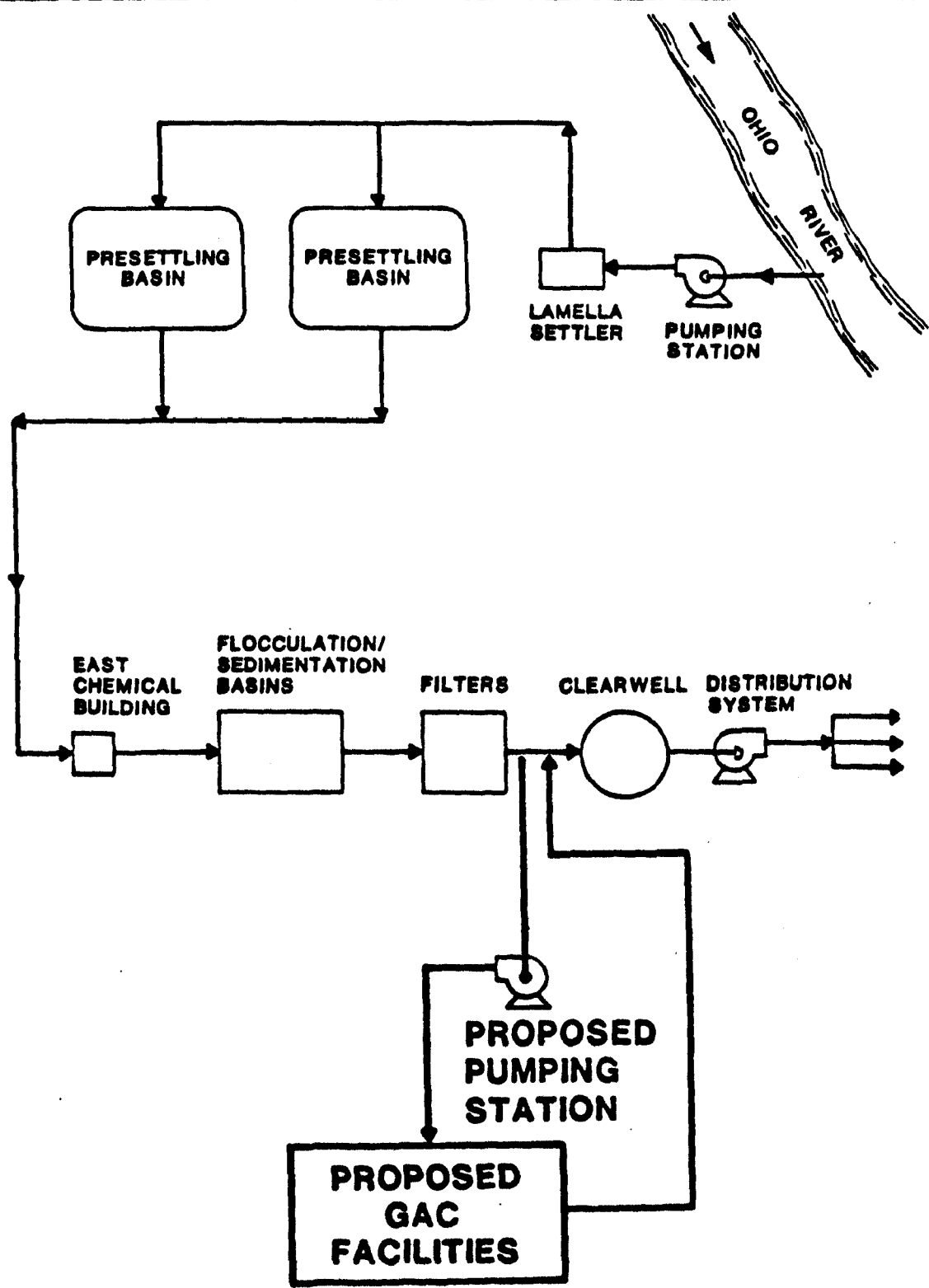
6. GAC design criteria:

Plant Flowrate (mgd):	
Annual Average	124
Maximum Day	175
Empty Bed Contact Time (min)	15
GAC Bed Depth (feet)	11
Maximum Loading Rate (gpm/sf)	5.5
Carbon Usage Rate (lb/day):	
Annual Average	54,000
Peak Period	92,000

7. Carbon contactor building layout - Figure II-6

8. Carbon contactor building floor plan - Figure II-7

9. GAC contactor cross sections - Figures II-8 and II-9

10. GAC transport system design

    a. all transport pipe is Schedule 10 316L stainless Steel

    b. bends

        3" pipe - 24" radius
        4" pipe - 36" radius
        8" pipe = 48" radius

    c. velocities - 3 to 5 fps

11. Regeneration System - see Figure II-10 for schematic of system

12. Capital Costs

    a. GAC Contactors
    b. Regeneration Equipment
    c. Intermediate Pumping Facilities
    d. Outside Piping
    e. Modification of Existing Facilities

    Capital Cost = $40 Million

13. O&M Costs

    a. Labor
    b. Power
    c. Natural Gas

335

INLET CHAMBER

EXISTING FILTER BUILDING

WEIR CHAMBER

FILTERED WATER

CARBON CONTACTED WATER

WASTEWATER DRAIN

CARBON CONTACTOR BUILDING

WASTEWATER RECOVERY TANK

OVERFLOW TO RIVER

336

CARBON CONTACTOR BUILDING LAYOUT

FIGURE II-8

CARBON CONTACTED WATER EFFLUENT

SEAL WELL (TYP.)

STORE ROOM

REGENERATION AREA

CARBON CONTACTORS

CARBON STORAGE

CARBON CONTACTORS

CARBON CONTACTORS

FILTERED WATER CLEARWELL (BEL.

CARBON CONTACTORS

FILTERED WATER INFLUENT

CARBON CONTACTOR BUILDING
FLOOR PLAN

FIGURE II-7

PIPE GALLERY

INFLUENT FLUME

EL.124.00

▽ WATER SURFACE EL.120.00

CARBON FILL PIPE

TOP OF CARBON EL.110.00

G. A. C.

BUTTERFLY VALVE (TYP.)

BACKWASH INFLUENT

EL.97.75

S. S. UNDERDRAIN HEADER

CARBON CONTACTED WATER

BACKWASH WASTEWATER DRAIN

GAC CONTACTOR SECTION

FIGURE 11-8

**GAC CONTACTOR
CROSS SECTION**

FIGURE II-8

REGENERATION SYSTEM SCHEMATIC

DEWATERED SPENT CARBON

CYCLONE

DRYER OFF-GAS

GRINDER

REGENERATION FURNACE

FURNACE OFF-GAS

RECYCLE

DRIED SPENT CARBON

AFTERBURNER

TO SCRUBBERS AND STACK

RECUPERATOR

340
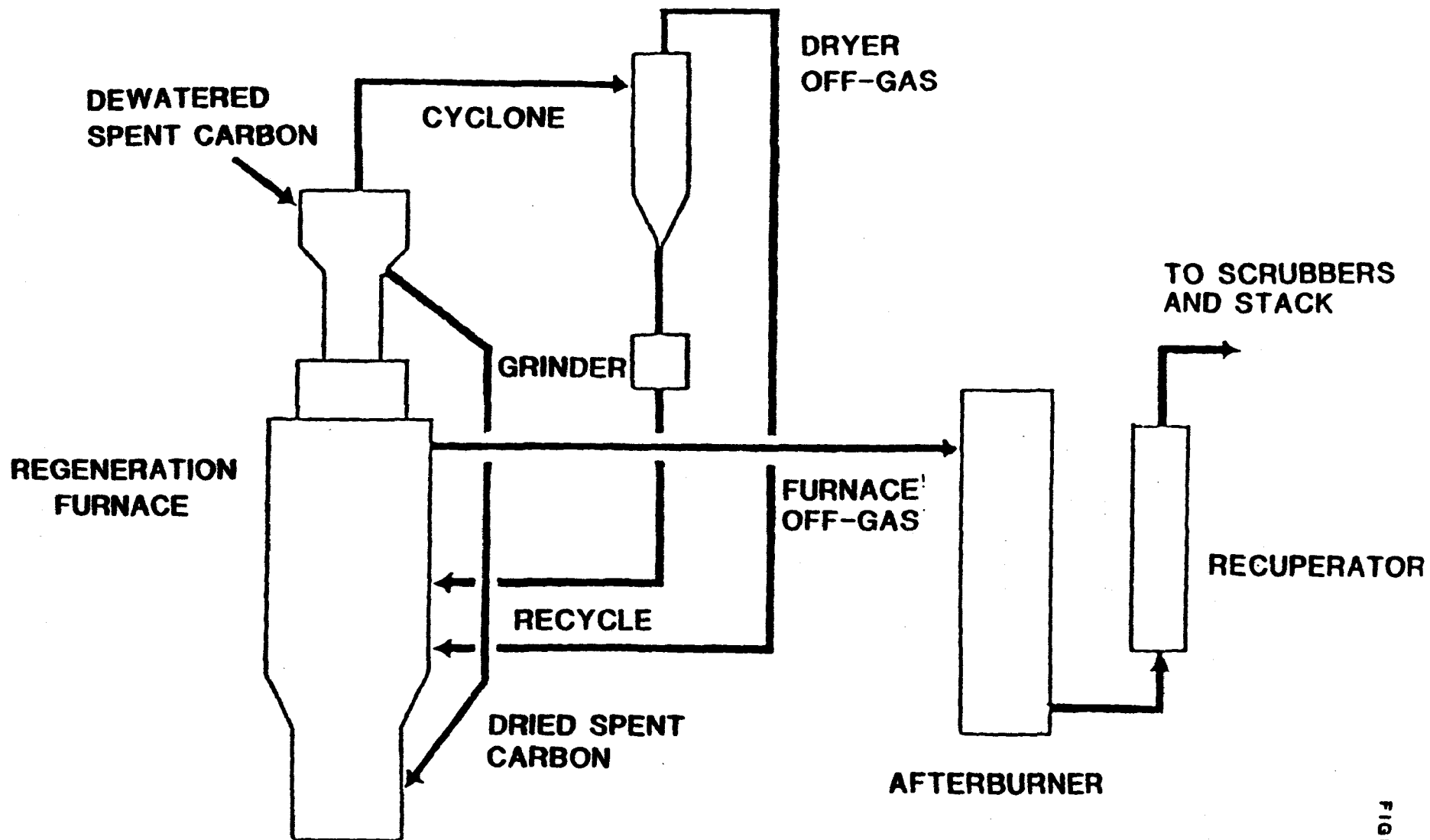
FIGURE II-10

d. Make-up GAC

    O&M Cost = $3 to 4 Million/yr

14. Cost Impact of GAC

    a. Average Bills Before Installation of GAC

        Quarterly: $ 8.10 for first 1,200 ft^3
                     10.80 for next 1,800 ft^3
                    $18.90   3,000 ft^3

        Annual: $80.00

    b. Projected Annual Bills After Installation of GAC

        -   If 30 percent increase, $80 + 30 percent = $105
        -   If 40 percent increase, $80 + 40 percent = $115

III. AERATION - TREATMENT OVERVIEW

Scope: Present a review of the use of aeration to remove organic chemicals
           from drinking water, including aeration principles, equipment,
           process design, facility design and costs.

A. PRINCIPLES OF AERATION

1. Rate of mass transfer proceeds according to following equation:

$$M = K_L a \Delta P$$

Where: M = mass of substance transferred per unit time and
              volume (lb/hr/cf)

        K_L = coefficient of mass transfer (lb/hr/sf)

        a = effective area (sf/cf)

        ΔP = concentration difference or driving force

2. Driving force is the difference between actual conditions in the air
    stripping unit and conditions associated with equilibrium between
    the gas and liquid phases. See Figure III-1 for example of driving
    force.

3. Equilibrium concentration follows Henry's Law, which states that the
    amount of gas that dissolves in a given quantity of liquid, at
    constant temperature and total pressure, is directly proportional to
    the partial pressure of the gas above the solution. Henry's con-
    stant calculated as follows:

    $$H \text{ (dimensionless units)} = \frac{(16.04)(P)(M)}{(T)(S)}$$

    P = vapor pressure in mm
    M = gram molecular weight of solute
    T = temperature in degrees Kelvin
    S = solubility in mg/L

4. A compound's Henry's Law constant indicates relative volatility of
    the compound; high Henry's Law constant - easily removed by air
    stripping.

FIGURE III-1
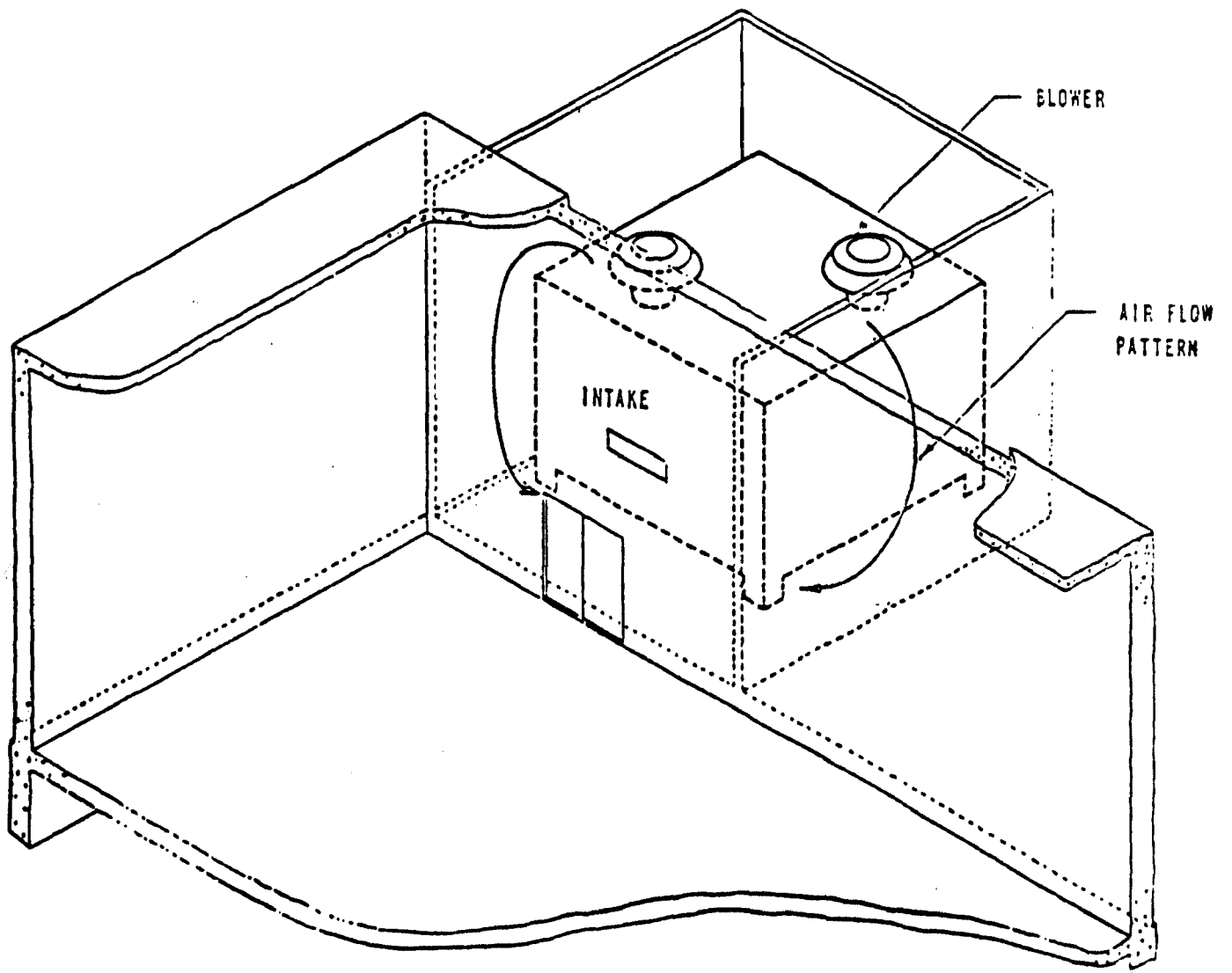
5. Henry's Constants for several organic chemicals:

    a. VOCs

                                                    Dimensionless Units

                    - Vinyl chloride: 285
                    - TCE: 0.44
                    - PCE: 0.88
                    - Cis-1,2-Dichloroethylene: 0.18

    b. Pesticides

                    - Aldicarb: 1×10^{-7}
                    - Chlordane: 0.015
                    - DBCP: 0.011

    c. Chlorinated Aromatics

                    - PCB: 0.021
                    - Dichlorobenzene: 0.086

B. AERATION EQUIPMENT

    1. Two types of aeration equipment:

        a. diffused air - inject air bubbles into water

        b. waterfall - cause water to fall through air

                    - Cascade
                    - Multiple tray
                    - Spray nozzles
                    - Packed column

    2. Diffused air system - Figure II-2 at end of this section is a
        diagram of diffused air basin.

    3. Waterfall Aerators

        a. Multiple tray - see Figure III-3 for diagram.

        b. Packed column - diagram of packed column is shown on Fig-
            ure III-4.

        c. Catenary grid unit - diagram shown on Figure III-5.

        d. Higee System - diagram shown on Figure III-6.

344

FIGURE III-2

DIFFUSED AIR BASIN

FIGURE II-3

INLET CHAMBER   AIR SEAL   WATER INLET   AIR OUTLET

DISTRIBUTOR NIPPLES

BAFFLES

AIR STACKS

STAGGERED SLAT TRAYS

AIR INLET

BLOWER

AIR SEAL   WATER OUTLET
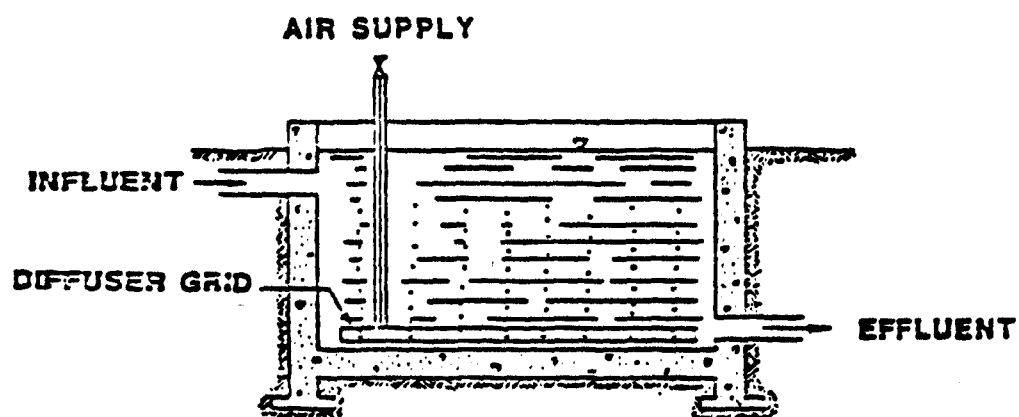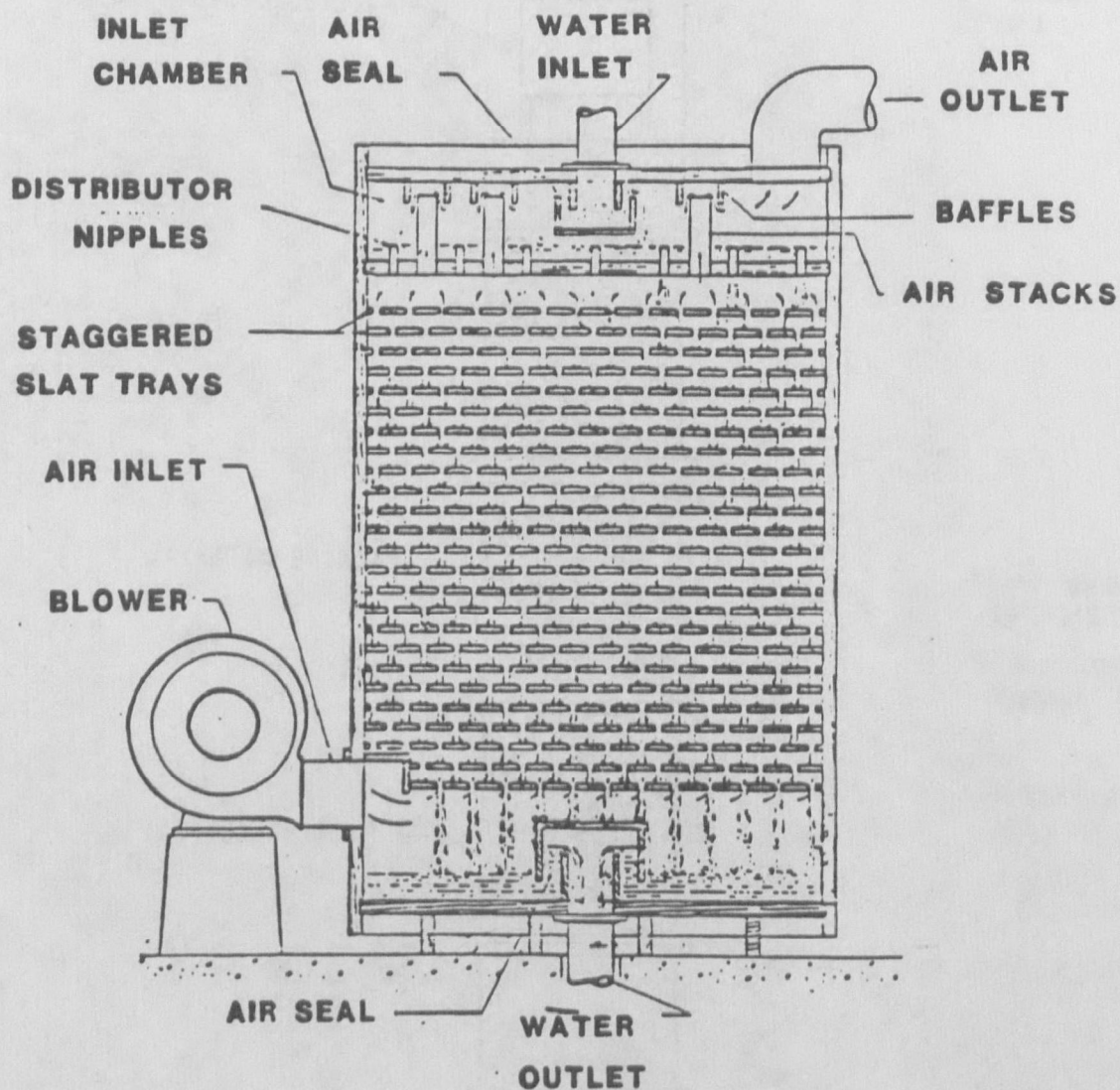
DIAGRAM OF A REDWOOD SLAT

TRAY AERATOR

FIGURE III-4

INFLUENT

LIQUID DISTRIBUTOR

PACKING MATERIAL

PACKING SUPPORT

AIR IN

EFFLUENT

DIAGRAM OF PACKED COLUMN

FIGURE III-5

DEMISTER

WATER INLET
(TYP.)

FLUIDIZED
ZONE

CATENARY
GRID (TYP.)

TREATED WATER
SAMPLE COLLECTOR

MANOMETER FOR
AIR FLOW RATE
MEASUREMENT

BLOWER

AIR FLOW
DAMPER

RAW WATER
ROTAMETER

RAW WATER
SAMPLE TAP

TREATED WATER
SAMPLE TRAP

WATER FLOW
METERING VAL

RAW WATER
FROM WELL

TREATED WATER
TO DRAIN

MALCOLM
PIRNIE

348

DIAGRAM OF PILOT-SCALE
CATENARY GRID UNIT

HIGEE SYSTEM

FIGURE III-6

C. PROCESS DESIGN CRITERIA

1. Diffused air system - improving process design:

    a. increase basin depth
    b. produce smaller air bubbles
    c. optimize basin geometry
    d. increase gas flow

2. Packed column design parameters:

    a. type of compound
    b. VOC concentrations (ug/L)
    c. type of packing material
    d. A:W ratio (cubic feet per cubic feet)
    e. Liquid loading rate (gpm/sf)
    f. Packing height (ft)
    g. water temperature

3. Figure III-7: effect of compound on packed column design

4. Figure III-8: effect of temperature on removal efficiency

D. FACILITY DESIGN CONSIDERATIONS
    (Packed Column Facility Components Shown on Figure III-9)

1. Design Considerations

    a. Location and site constraint
    b. Noise
    c. Aesthetics
    d. Housing and type of construction
    e. Air quality
    f. System hydraulics
    g. Instrumentation and control
    h. Column and column internals
    i. Clogging of packing

2. Location/Site Constraints

    a. Zoning requirements
    b. Height restrictions
    c. Location of air intake louvers

3. System Hydraulics

    a. Restaging well pumps
    b. Flow and system pressure
    c. Repumping to distribution system

350

EFFECT OF COMPOUND ON PACKED COLUMN DESIGN

95% REMOVAL

55°F

CHLOROFORM

1,2 DICHLOROETHANE

TCE

PACKING DEPTH (FT.)

A/W RATIO

FIGURE III-7
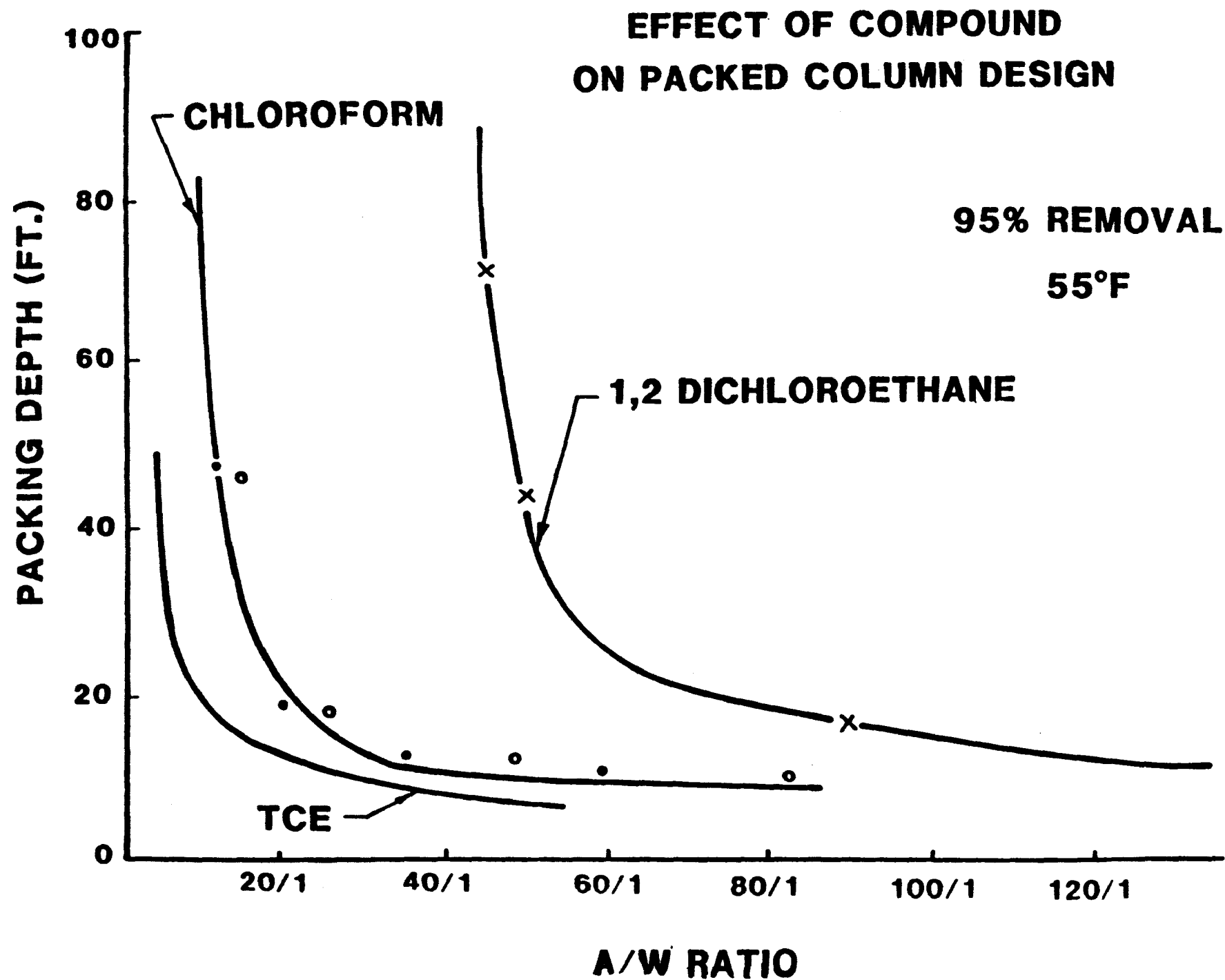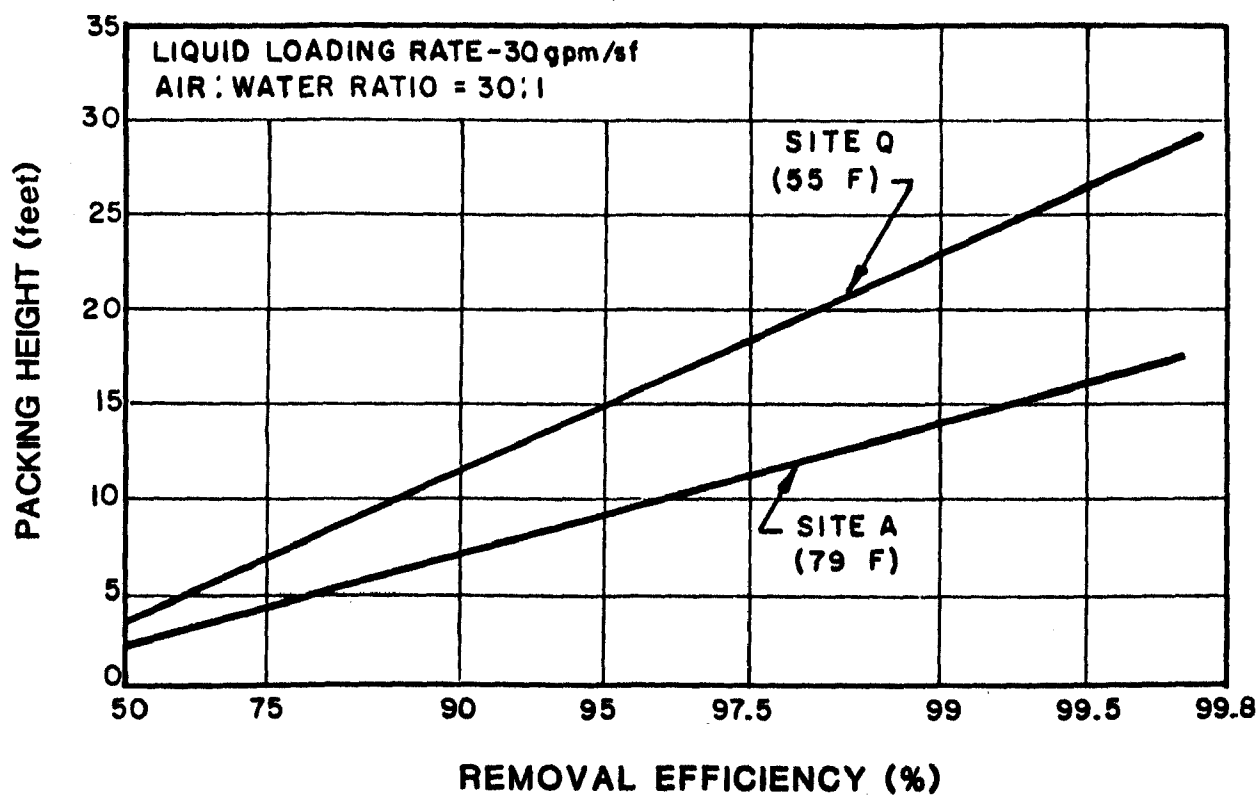
FIGURE III-8

PACKING HEIGHT VS REMOVAL EFFICIENCY
TCE
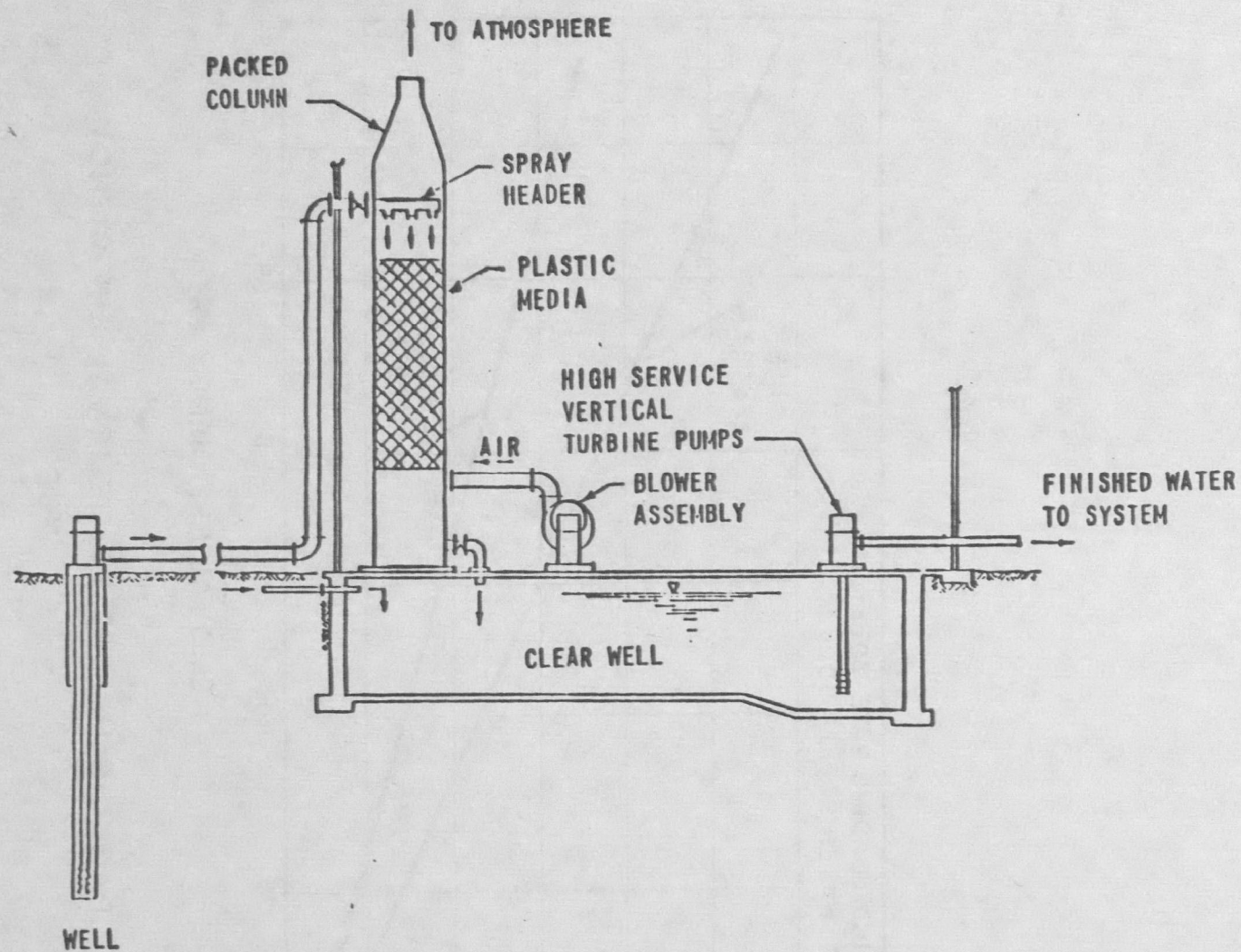
PACKED COLUMN SYSTEM COMPONENTS

TO ATMOSPHERE

PACKED COLUMN

SPRAY HEADER

PLASTIC MEDIA

HIGH SERVICE VERTICAL TURBINE PUMPS

AIR

BLOWER ASSEMBLY

FINISHED WATER TO SYSTEM

CLEAR WELL

WELL

FIGURE III-9

4. Housing

   a. Freezing potential (see Figure III-10 for examples of temperature effects on aeration system)

   b. Noise

   c. Security

   d. Equipment maintenance

5. Column and Column Internals

   a. Column Construction

      - FRP (fiberglass-reinforced plastic)
      - Aluminum
      - Stainless steel
      - Concrete

   b. Mist eliminator

   c. Liquid distributor

      - orifice plate (see Figure III-11)
      - trough-type distributor (see Figure III-12)
      - orifice headers
      - spray nozzles

   d. Support grid

   e. Packing Media

6. Air Quality

   a. Intake air - air-bourne contaminants
   b. Exist air - discharge regulations

7. VOC Emissions

   a. Discharge rate - pound/hour

   b. Ambient concentrations

   c. Modeling

   d. Column modifications

      - Height
      - Air flowrate
      - Exist velocity

FIGURE III-10

TEMPERATURE EFFECTS
ON AERATION SYSTEM – JANUARY 1983

WATER IN
51°F

AIR OUT

AMBIENT AIR
18°F

WATER OUT
49°F

AIR IN
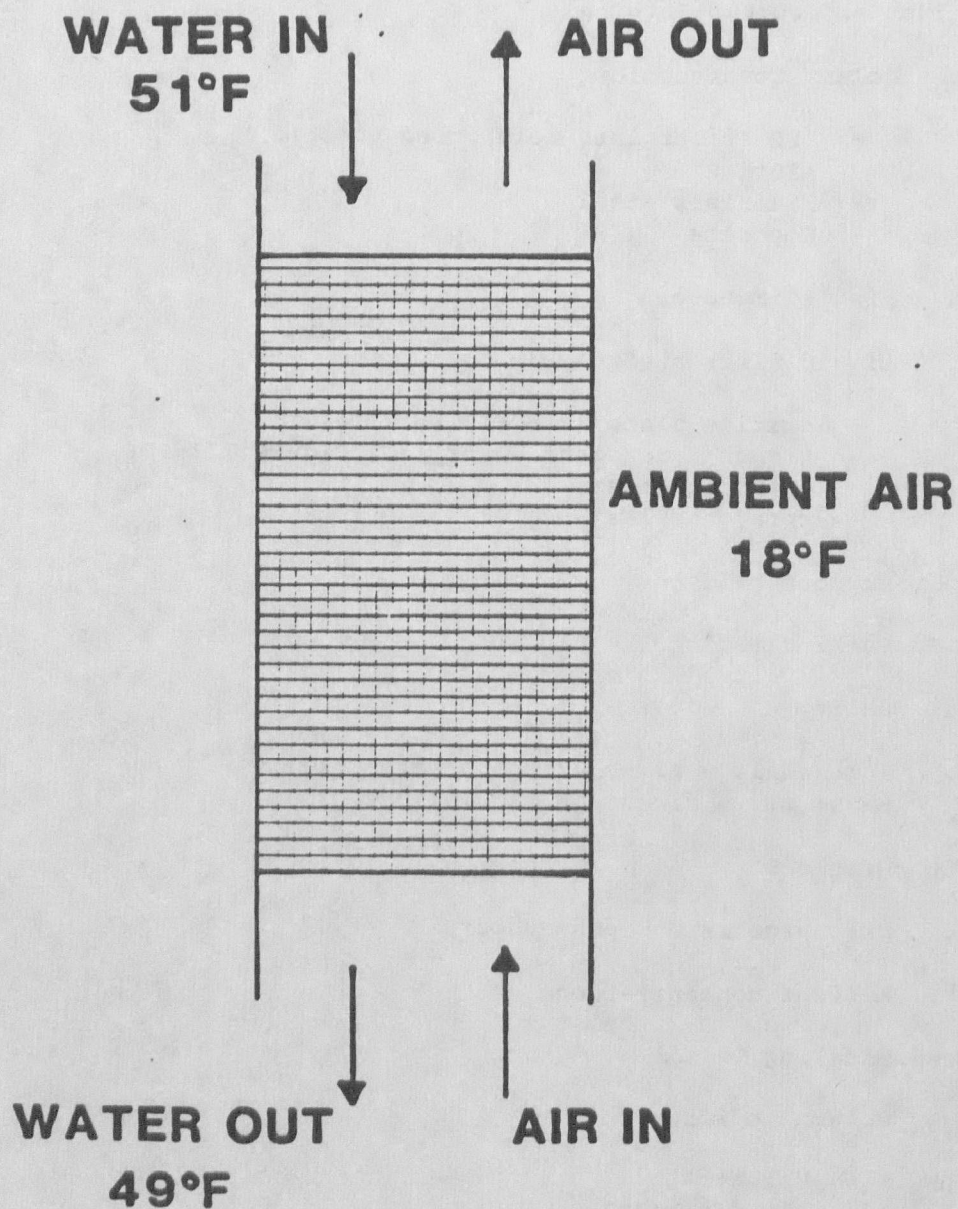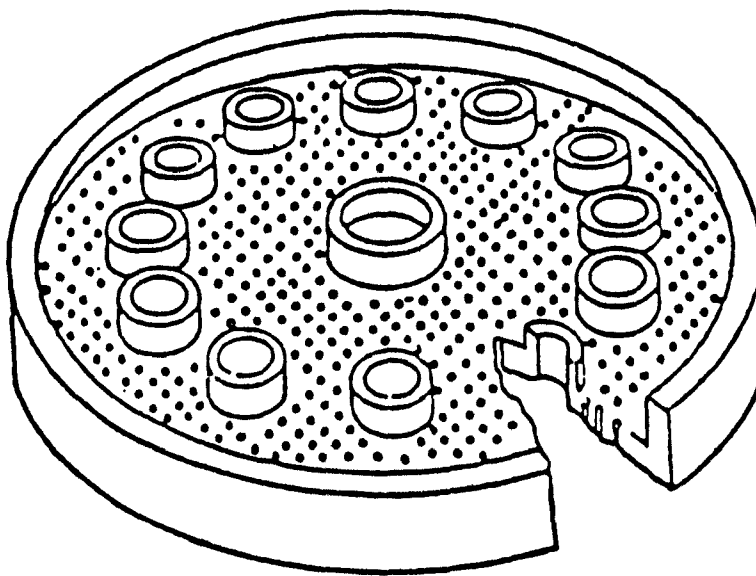
FIGURE III-11

Orifice - type distributor
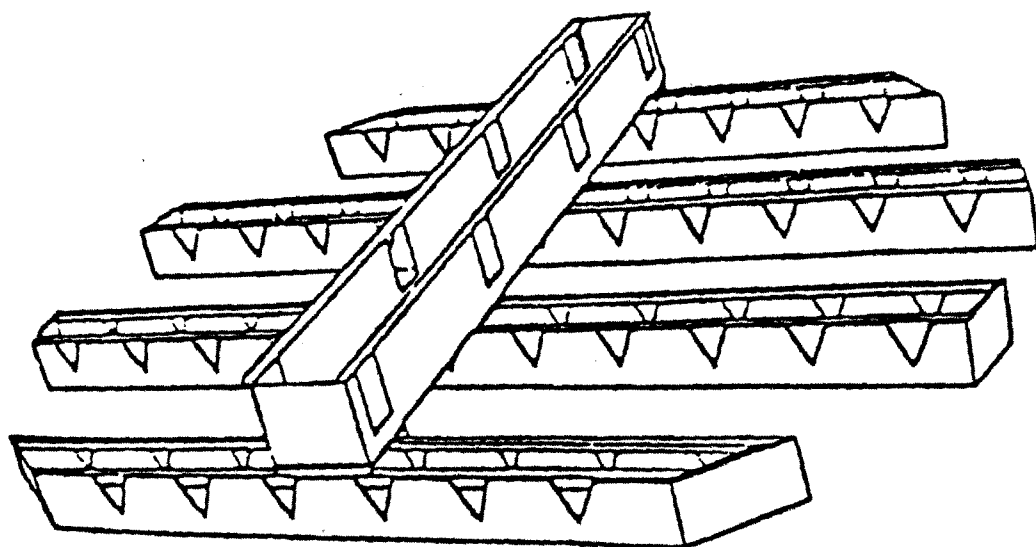
FIGURE III-12

Trough-type distributor

      e.   Vapor phase carbon (see Figure III-13)

  8.   Clogging of Packing

      a.   Iron

      b.   Solids

      c.   Biological growth

      d.   Pretreatment requirements may have to be considered for any one of these problems

  9.   Corrosivity of Treated Water

      a.   Problem: increase DO, reduce CO_2
      b.   Solution: reduce pH; provide post treatment

E.   ECONOMICS

  1.   Packed column cost components.

Basic	Site Specific
Column Structure	Special sitework
Internals	Raw water holding tank
Packing	New/restaged well pump
Blower(s)	Blower building
Clearwell	Booster pump building
Booster pump(s)	Chemical facility
Piping	Noise control installation
	Air emissions control

  2.   Capital costs of packed columns - see Figure III-14.

  3.   O&M costs of packed columns - see Figure III-15.

  4.   Relative costs for removal:

     Vinyl Chloride   —   least costly to remove
     PCE
     TCE
     Carbon Tetrachloride
     1,2-Dichloroethane
     DBCP   —   most costly to remove
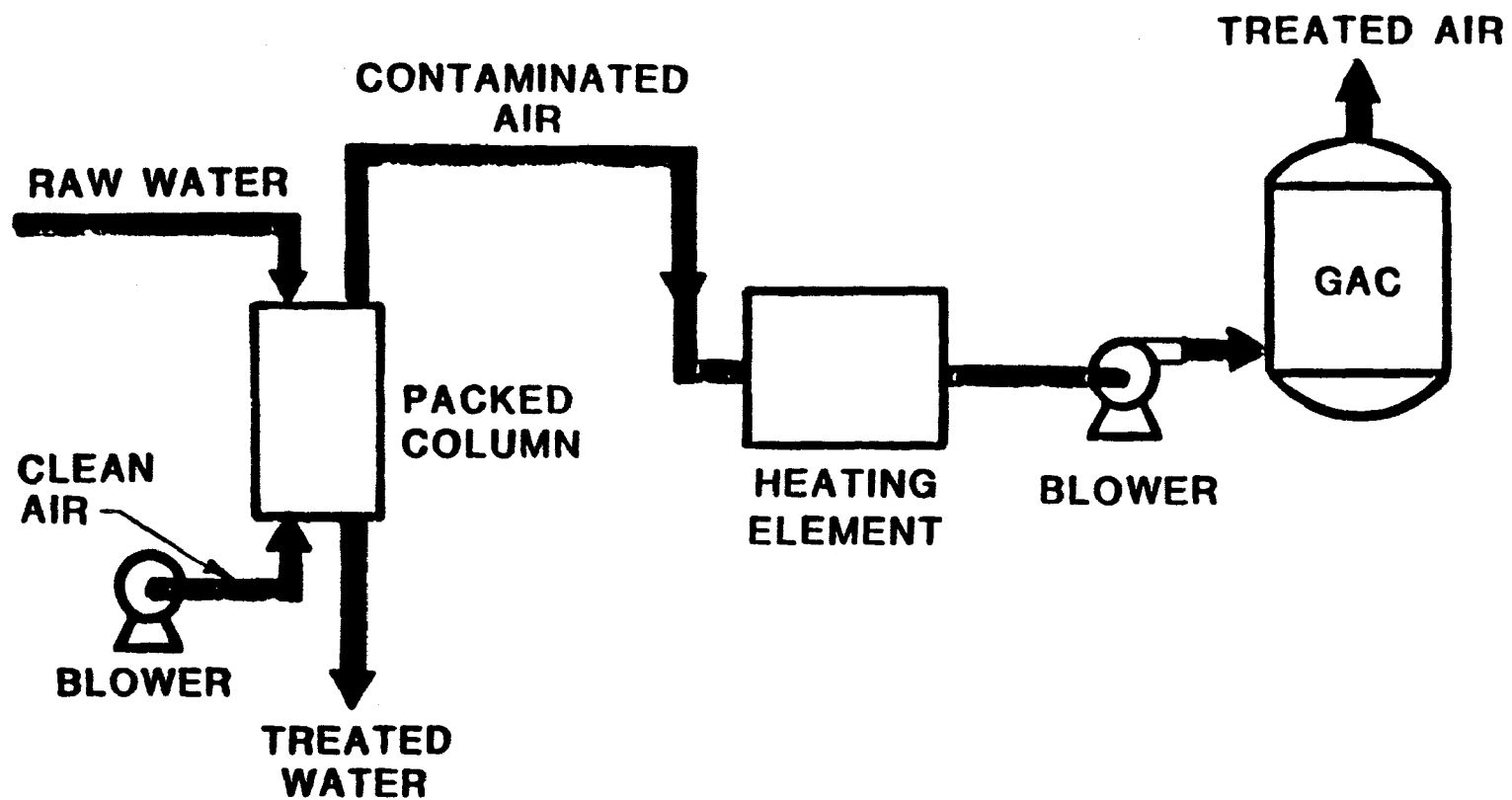
VAPOR PHASE CARBON

FIGURE III-13

ANNUAL O&M COSTS
FOR PACKED COLUMN SYSTEMS

FIGURE III-14

ANNUAL O&M COSTS
FOR PACKED COLUMN SYSTEMS

FIGURE III—15
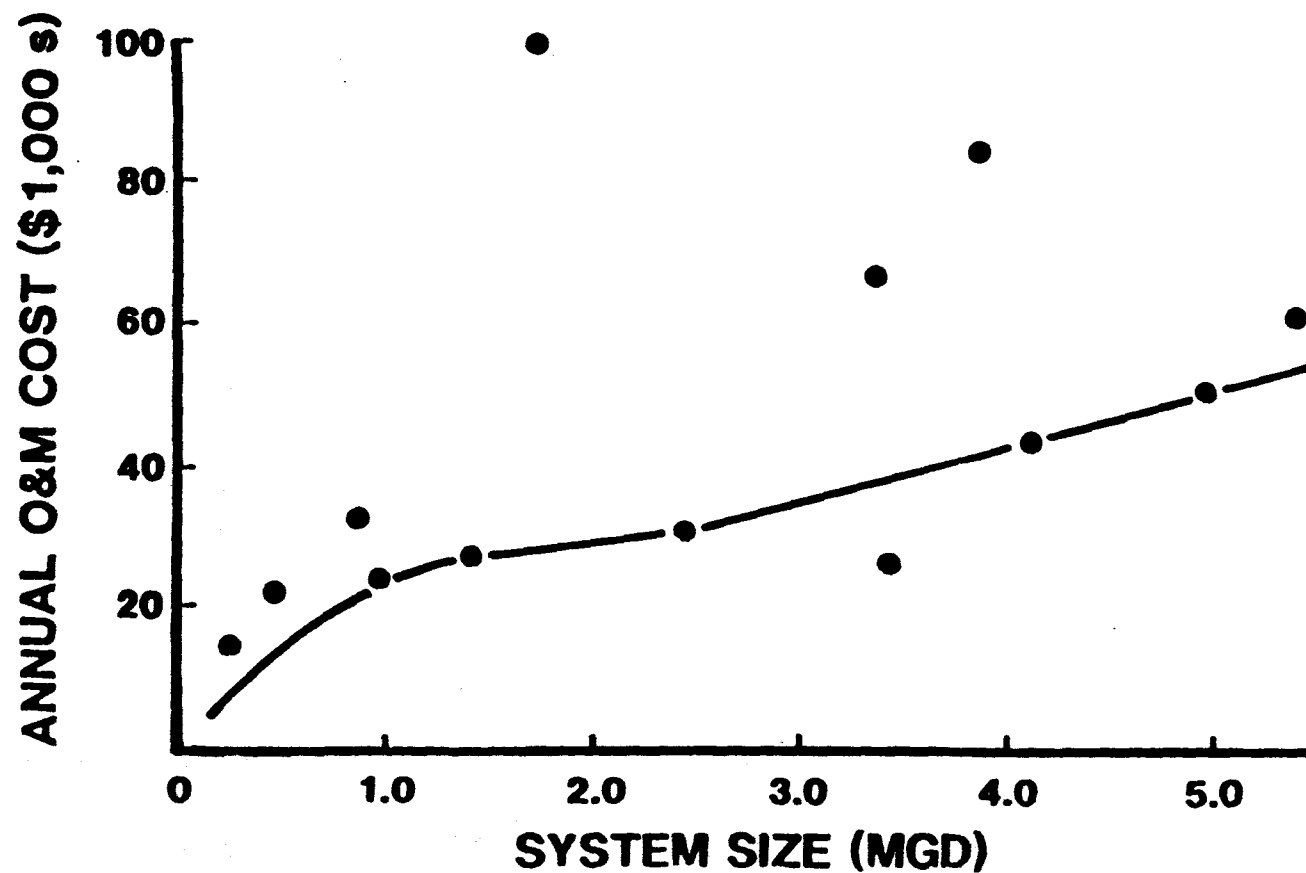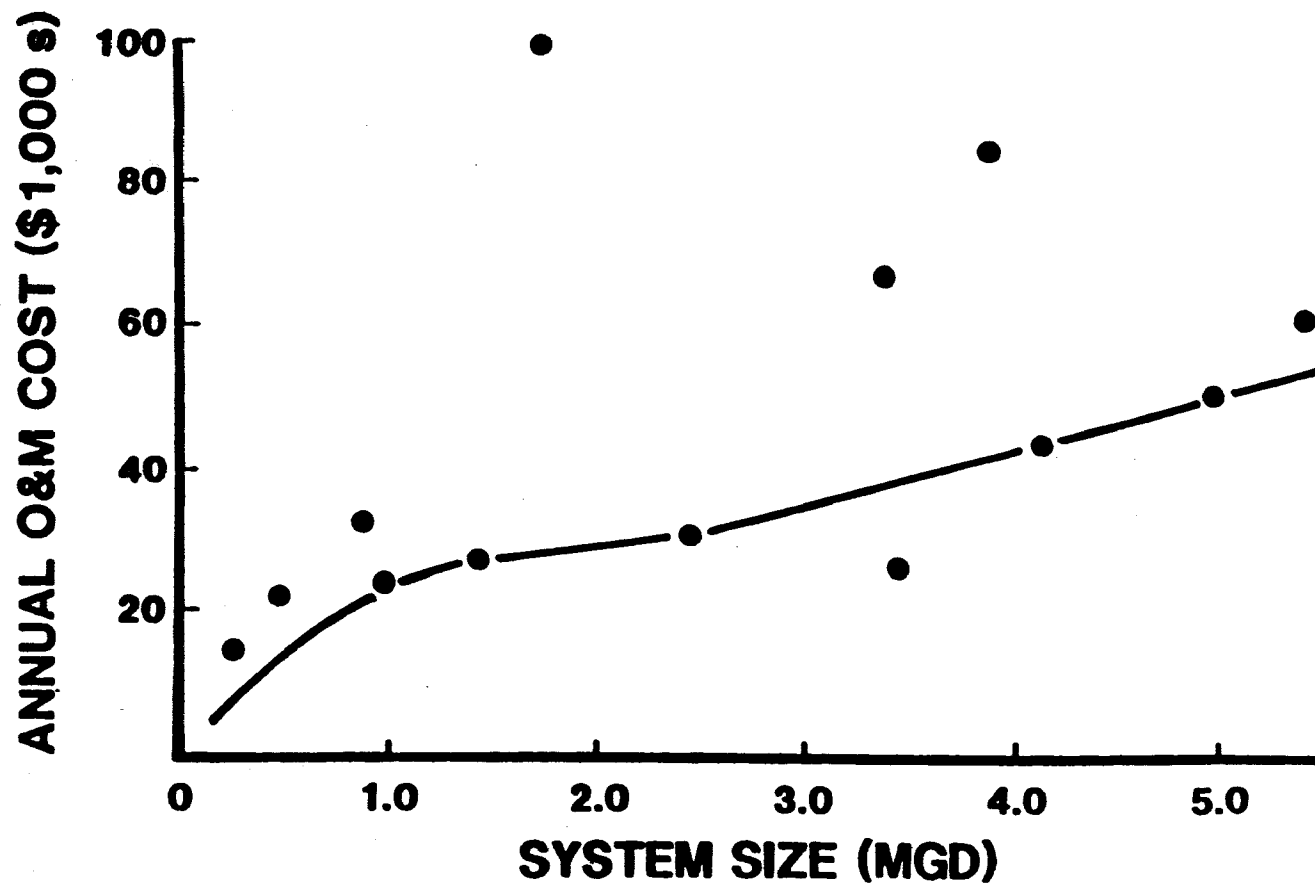
IV. AERATION - CASE STUDY

Scope: Describes experience of a water supplier in dealing with organic contamination of its supply using packed column aeration.

A. PACKED COLUMN AERATION - SCOTTSDALE, ARIZONA

1. System Characteristics

    - ground water supply
    - 24 wells
    - 40 mgd capacity

2. Water Quality

    a. Well No. 6 (1,200 gpm), TCE: 18 to 200 ug/L

    b. Well No. 31 (2,500 gpm), TCE: 5 to 43 ug/L

3. Evaluation of Alternatives

    a. GAC adsorption - $0.17 - 0.38/1,000 gal.
    b. packed column aeration - $0.07/1,000 gal.

4. Pilot tests conducted on-site to evaluate packed column aeration; mini-column tests conducted in laboratory to evaluate GAC adsorption

5. Design Considerations

    a. TCE removal
    b. Air quality
    c. Aesthetics
    d. Noise

6. Process Design Criteria

    a. Flow: 1,200 gpm
    b. Packing Height: 12 feet
    c. A:W Ratio: 50:1
    d. Column Diameter: 10 feet
    e. Removal Efficiency: 97 percent of TCE

7. Facility Schematic - see Figure IV-1

8. Facility Layout - see Figure IV-2

9. Air Quality Monitoring Study

    a. review local meteorological conditions
    b. simulate impact of packed column operation

EXHAUST
AIR

INFLUENT
WATER

WELL NO.6

TREATED WATER
TO RESERVOIR

BOOSTER
PUMP

BLOWER

CLEARWELL
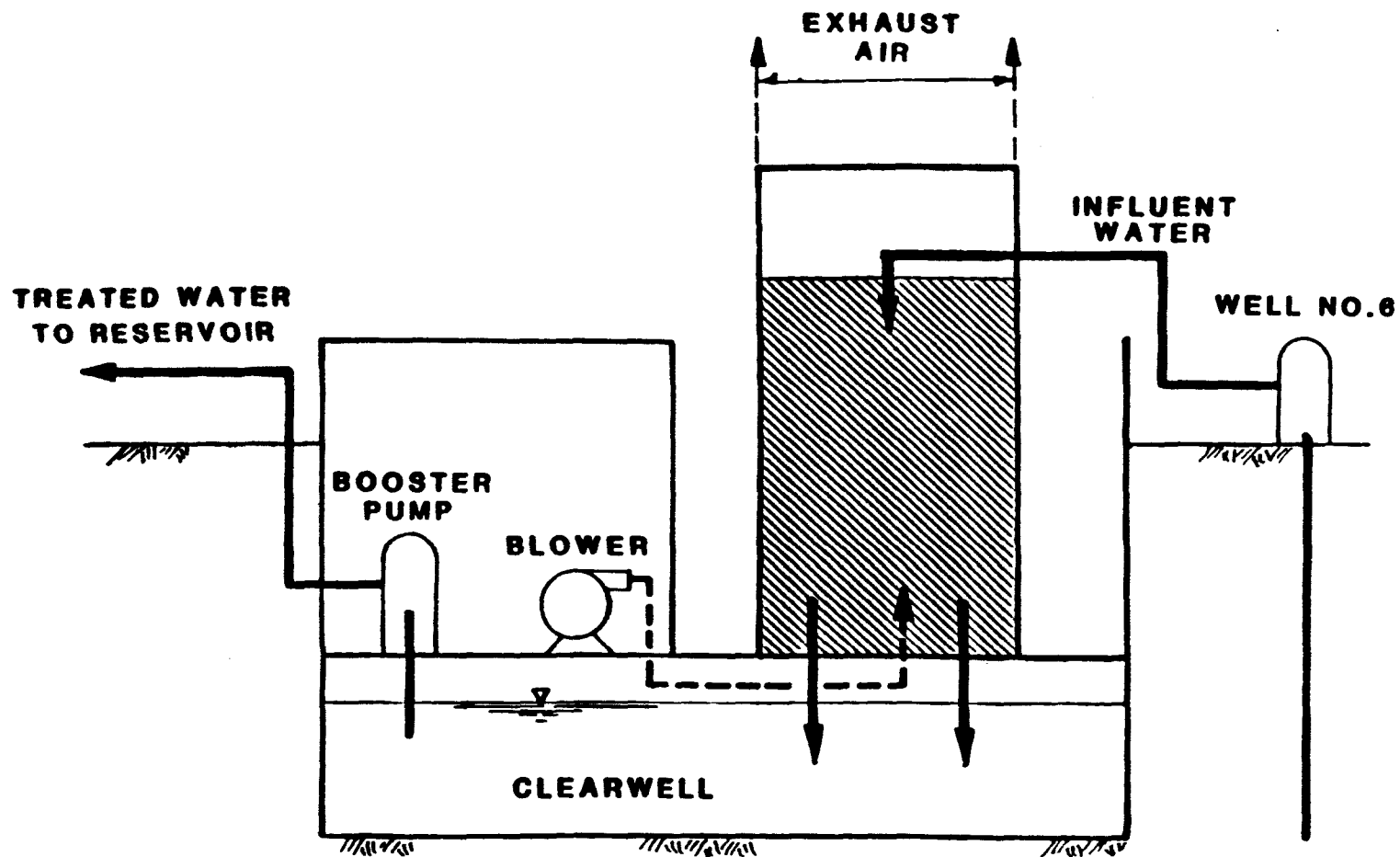
SCHEMATIC DIAGRAM
SCOTTSDALE PACKED COLUMN

FIGURE IV-1

SCOTTSDALE FACILITY LAYOUT
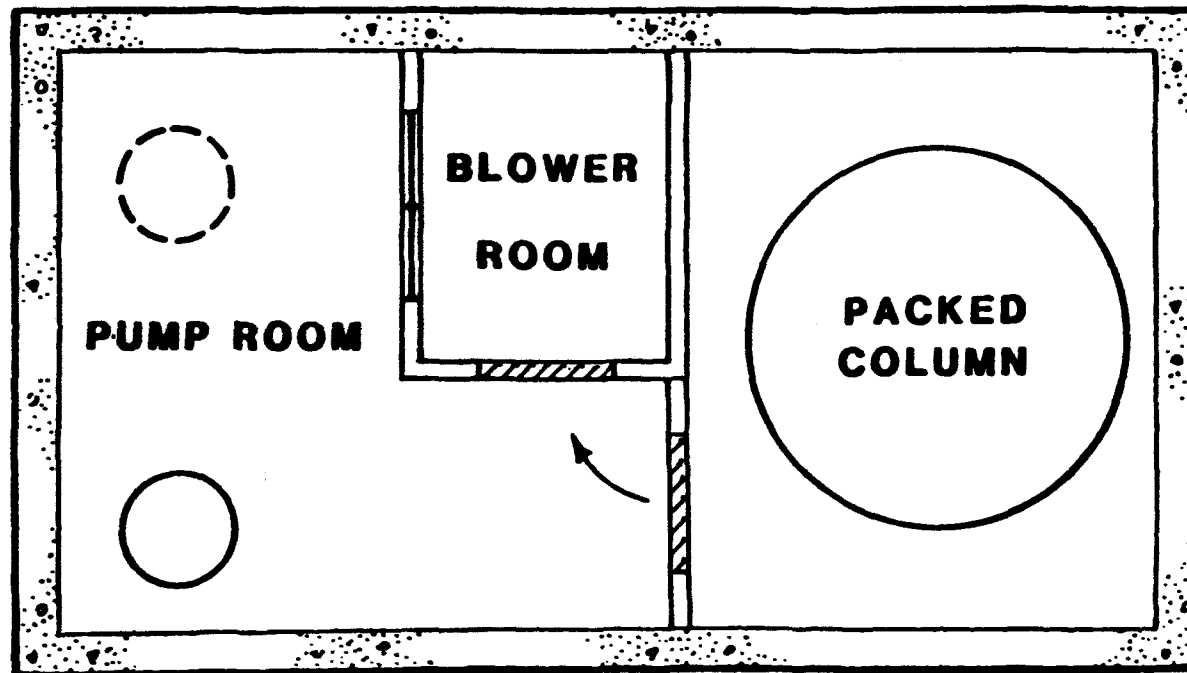
FIGURE IV-2

c.   establish background TCE levels
d.   monitor air quality during operation
e.   recommend long-term monitoring program

10.   Proposed Packed Column Operating Schedule (see Figure IV-3).

11.   Air Quality Monitoring

Date	Weather Conditions	Distance Downwind (m)	TCE Concentration (ug/m^3)
2/20/85	Sunny, breezy	20	<0.01
		48	<0.01
3/6/85	Overcast, calm	16	0.05
		48	0.04
		61	<0.01
		95	<0.01

12.   Full-scale Operating Results

Date	TCE Concentration (ug/L) Influent	Effluent	Percent Removed [1]
2/20/85	67.3	0.5	99.3
3/6/85	89.1	1.1	98.7
3/17/85	190	1.1	99.4
3/19/85	200	1.2	99.4

(1)   Design percent removal = 97%.

13.   Costs

a.   Capital: $300,000
b.   O&M: $25,000/year

14.   Interaction with Public

a.   media coverage
b.   public meeting
c.   formation of citizen groups
d.   tour of facilities
e.   recommendations of citizen groups

15.   Conclusions

a.   Packed column aeration is effective
b.   Obtain public comment early
c.   Encourage positive media coverage
d.   Be prepared to address air quality impacts

CITY OF SCOTTSDALE
PROPOSED PACKED COLUMN
OPERATING SCHEDULE

FIGURE IV-3

366
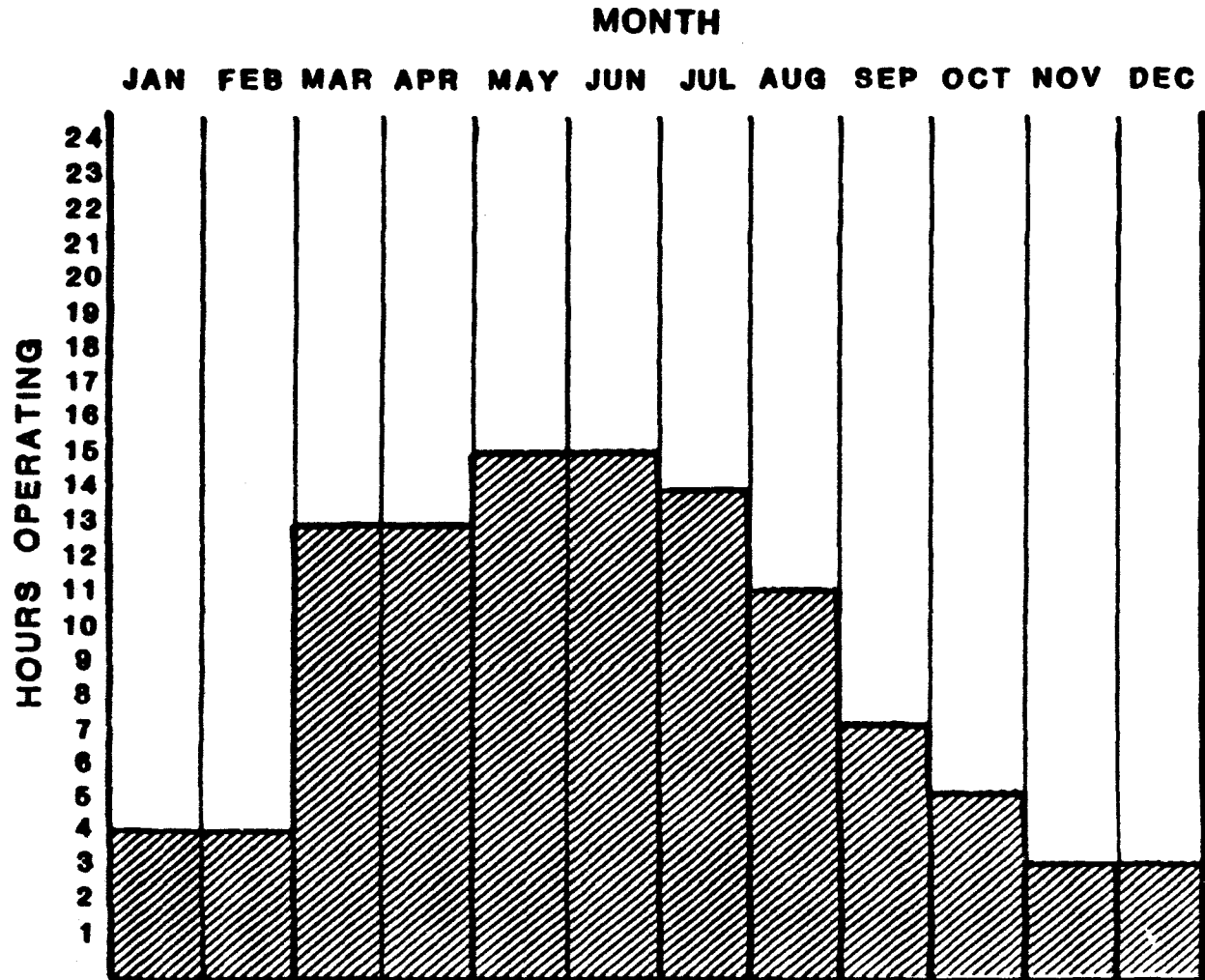
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D.

RISK MANAGEMENT PROBLEM

GROUNDWATER CONTAMINATED WITH ALDICARB,
TRICHLOROETHYLENE AND VINYL CHLORIDE

RISK MANAGEMENT CASE STUDY

Introduction to Case Study

I. Background Information on Aldicarb, Trichloroethylene and Vinyl Chloride

II. Drinking Water Regulations: Statutory and Institutional Background

III. Background on the Water Supply System

IV. Calculating Human Exposure and Risk

V. Options for Reducing Risks

INTRODUCTION TO THE RISK MANAGEMENT CASE STUDY

You are a group of experts called together by the water supply manager of a small town to advise her on a possible case of drinking water contamination. You will be required to analyze the situation and make a brief presentation of your findings at a public meeting. Earlier you were presented with information concerning the health risks associated with exposure to the three compounds. You are aware that, although the risk assessment is fairly complete, there are a host of other factors that must be considered in implementing a permanent solution. These factors will be a part of your risk managment problem. While risk assessment considers the nature of the risk, risk management must consider taking appropriate action to alleviate that risk.

Most of you probably are familiar with the work of Dr. John Snow in London, 1854. Dr. Snow, through a very thorough epidemiological study, proved that the Broad Street pump was the source of an outbreak of cholera. He did this by statistically correlating incidence of disease with exposure to drinking water at that well. This example was an early form of risk assessment. Later, Snow removed the handle from the pump and observed that, as the people drank water from other sources, the incidence of cholera declined. This later act was what we are calling risk management. Dr. Snow took positive action to correct the problem. Unfortunately, today's drinking water contamination problems are not solved as readily.

Snow had a relatively simple problem to solve by modern standards, but remember, he accomplished this twenty years prior to the discovery of the germ theory of disease by Koch and Pasteur. The public health aspect of drinking water has come upon the reverse of Snow's problem. He knew the risk of drinking water from the Broad Street Pump, but could not identify the contaminant.

Today we can identify many more contaminants, but are unable to determine the exact nature of the potential adverse human health effects. Further, quantifying those risks is itself a risky business. Projection of human risk exposure from data on animal carcinogens would appear to be straight forward. But, as you saw in the risk assessment problem, even the "experts" cannot agree on validity of extrapolation of animal data to human health risks. Even the most experienced scientists cannot predict the exact nature of the risk of exposure to chemical contaminants.

In the problem described here, the risk assessment would likely conclude that one contaminant is an animal carcinogen, another, a human carcinogen, and the third, a neurotoxin. Large uncertainties surround the projection of human risks from animal data. Six or more orders of magnitude (10^6 or one million times) of uncertainty are associated with the use of models extrapolating animal data to human data. Everyone would feel more comfortable if there were more certainty in the risk assessment, but there is very seldom a straight answer to a chemical contaminant safety issue. All of this uncertainty becomes part of the evaluation and analysis conducted in the process called risk management.

YOUR ROLE

You, as an expert consultant, must advise the town manager and recommend an appropriate course of action to protect the public health, both long and short term. Specifically, you are concerned with mitigating people's exposure to the toxic chemicals in drinking water.

This case study focuses on your ability to use the information presented in this course to solve a drinking water contamination problem. The review and evaluaton will take place with a group of 10 to 15 people. You will realize that there is no one right or wrong answer and common sense should prevail. The process by which you arrive at your conclusions is very important. The group should attempt to come to a concensus about what action can be taken. If you cannot come to a concensus, present the alternative views. The conclusions of each work group will be compared and contrasted at a final plenary session.

NATURE OF THE MATERIAL

You will focus on several types of information. Results of the previously completed risk assessments will be reviewed briefly. In addition, both qualitative and quantitative information will be provided on various courses of action. This information will include political and social factors as well as treatment, economic and environmental data. You must consider the interests of various economic and public interest groups in your recommendation.

The case study package is divided into five sections. Each package also contains the Health Advisory documents for aldicarb, vinyl chloride and trichloroethylene. The Health Advisory documents contain occurrence, health effects, analytical chemistry and treatment data on each chemical. Use this information as appropriate in formulating your respose to the questions that appear in the latter sections of the case study. The discussion of drinking water regulations focuses on proposed rulemaking for the volatile synthetic organic chemicals and some pertinent legislative background. This information should prove useful in organizing your thoughts, but should not be viewed as providing the exact answer or constraining your response. Remember, this is proposed rulemaking and you are required to respond immediately. The following three sections provide site-specific information, questions to be answered and calculations to be performed. It might be helpful if someone in each group could provide a calculator, but this is not required. We also will provide a facilitator for each group. He should not lecture, nor should you look to him for providing answers.

The focus of this exercise is risk management and risk communication. Try to use the conclusions from your risk assessment of the relevant chemicals, as well as the information provided here and in the lectures.

I. BACKGROUND INFORMATION ON CHEMICALS

        The Health Advisories for aldicarb, trichloroethylene and vinyl
chloride are located in this workbook in the next section immediately
following this problem. Additional information concerning the chemicals
will appear as appropriate throughout this document and in some of the
lecture outlines.

II. DRINKING WATER REGULATIONS: STATUTORY AND INSTITUTIONAL CONCERNS

INTRODUCTION

In thinking about how to manage a drinking water contamination incident it would be useful to understand the framework provided by the Safe Drinking Water Act as amended through 1986. This Act provides a two step approach to setting drinking water standards. The first step is to set a maximum contaminant level goal (MCLG), formerly called the recommended maximum contaminant level (RMCL). EPA must also set the maximum contaminant level (MCL) as close to the MCLG as is feasible. Simply put, MCLGs are health-based goals and MCLs are technologybased standards. Standards are enforceable and goals are not.

MCLGs are non-enforcable health goals. MCLGs are "set at the level at which no known or anticipated adverse effects on the health of persons occur and which allow an adequate margin of safety". The House Report on the Safe Drinking Water Act provides Congressional guidance on developing RMCLs (MCLGs):

> "... the recommended maximum level must be set to prevent the occurence of any known or anticipated adverse effect. It must include an adequate margin of safety, unless there is no safe threshold for a contaminant. In such a case, the recommended maximum contaminant level should be set at zero level".

The RMCLs (MCLGs) for a number of carcinogenic volatile organic chemicals were proposed at zero based on this language. Obviously, the MCL or enforceable level cannot be zero since zero cannot be measured. The MCL or enforceable level must be a non-zero number.

The MCL must be set as close to the RMCL (MCLG) as is feasible. Feasible means with the use of the best technology, treatment techniques and other means available taking cost into consideration. The 1986 Amendments include language indicating that these technologies must be tested under field conditions. The Amendments also state that technologies, for the control of synthetic organic chemicals (SOCs), must be at least as effective as granular activated carbon.

The general approach used in setting MCLs for the volatile organic chemicals (VOCs) or any other contaminant is to determine feasibility. This requires an evaluation of: (1) the availability and cost of analytical methods, (2) the availability and performance of treatment technologies and (3) an evaluation of the cost and feasibility of achieving various levels. A brief non-technical description of each component of the regulatory analysis follows.

ANALYTICAL METHODS

The analytical method constraints include considerations of precision and accuracy at low (ppb-part per billion) levels. The numbers produced by the analyst must be within some reasonable proximity of the true value (accuracy) and must be reproducible (precision).

The analytical methods for the volatile organic chemicals include gas chromatography (GC) with either conventional detectors or a mass spectrometer (GC/MS). These analytical methods use the purge and trap technique for extraction from the liquid phase and concentration on a columnn containing a sorbent. The higher molecular weight organic chemicals (e.g., pesticides) generally require extraction with a solvent (e.g., hexane or methylene chloride). The sample or solvent extract is injected into the entrance port of the GC column. Purging of the volatile chemicals is accomplished using an inert gas. The organic chemicals of interest are then sorbed to the wall or special packing material within the column. The compounds are desorbed from the column by heating and backflushed into the head of the GC column. This is followed by separation of constituents in the GC column and measurement with a specific detection system. Detection systems include photo-ionization and electrolytic conductivity. The detection system generates an electrical signal which is amplified and transformed to a peak on a strip chart recorder. The position and height of the peak is then compared to internal standards for identification and quantification.

Each step of this process is subject to some error. These errors are expressed as precision and accuracy. For the single lab this is sufficient. But, in developing national standards, one must consider interlaboratory variablity. In general, EPA defines the method detection limit (MDL) as the minimum concentration of a substance that can be measured and reported with 99 percent confidence that the true value is not zero. This detection limit differs for different labs, different instruments, different analysts, and is not necessarily reproducible over time if all these factors remain the same. Traditionally, quantification limits are five to ten times the method detection limit. The importance of this is that it is not possible to determine compliance or noncompliance with an MCL unless there is reasonable assurance that the reported value is close to the true value.

The remaining component of the use of analytical measurements in solving drinking water contamination problems is that of acceptable laboratory performance. The criteria for EPA certified labs for the types of gas chromatography (GC) analyses under consideration in this problem are ± 40% at concentrations under 10 ug/L and ± 20% at concentrations above 100 ug/L. Consider these limitations in determining what levels will be acceptable in solving the case study problem.

TREATMENT TECHNOLOGIES

Once the lowest level that can be quantified has been determined, the next constraint for determination of the MCL is the performance of the Best Available Technologies (BAT). The obvious first step would be to list all technologies that have ever been used to remove a particlar compound or class of contaminants. For example, for the volatile organic chemicals, there are data available on ozonation, ultraviolet irradiation, aeration and adsorption. Conventional coagulation and softening treatment provides little to no removal of these compounds. However, there is limited evidence that ozonation and ultraviolet irradiation can break down chlorinated ethylenes and other organic molecules with double bonds. The kinetics of oxidation of organic contaminants is not understood well enough to determine the cost of various levels of removal.

Packed tower aeration and, to a lesser extent, granular activated carbon (GAC) adsorption have been shown to be highly effective (>99.9% removal) for the removal of volatile organic chemicals. The BAT determination for the volatile organic chemicals is then based on these two processes.

Aeration Treatment

The performance potential of a properly designed packed tower aeration system is quite good for VOC removal. Both field and laboratory experiments and theoretical calculations indicate that at the concentrations generally found in drinking water (a few hundred parts per billion or less) aeration can produce treated water with sub-part per billion concentrations. Aeration processes provide a fixed percent removal of contaminants. As a consequence the concentration in the treated water can be affected by fluctuations in the raw water concentration. Volatile organic chemical contamination of ground waters is generally due to poor waste disposal practices and many times the exact source can never be found. The hydrogeological factors affecting the fate and transport of these chemicals are complex. Modeling them is an inexact science. As a result, historic information on changes in concentrations should be considered in the design of an aeration treatment system. Traditionally, a safety factor of two times the raw water concentration has be used in a conservative design. If these and other design factors are properly considered, the treated water should meet a concentration goal below the analytical quantification levels.

Transfer of volatile organic chemicals from air to water might be a concern depending on the proximity to human habitation, treatment plant worker exposure, local air quality, local meteorological conditions, daily volume of water processed and the concentration of the contaminant. EPA evaluated a number of existing and planned packed tower installations using an air dispersion/human exposure model. The results of this evaluation indicated that lifetime exposure to small amounts of carcinogenic chemicals in air did not result in a significant increase in individual risk of cancer (generally, less than one in 10^6 or 10^7). These were the highest risks and occurred for persons exposed to 70 years of worst case air concentration conditions at less than two hundred meters from the source. As the distance grows, the population exposed increases, but the concentration declines so rapidly that projected cancer risks become very small. Using very conservative assumptions these kinds of analyses resulted in a projection of less than one possible cancer incidence nation-wide over seventy years. Since drinking water contaminated with the carcinogenic chemicals of concern was the projected cause of approximately 50 excess cases of cancer, one could conclude that air emissions from aeration treatment facilities are not a major national concern.

If necessary, control of volatile organic chemical emissions from packed tower aeration installations is feasible using air phase GAC adsorption. EPA currently has full-scale field evaluations of this technology under way. Preliminary evidence indicates that installation of this equipment would approximately double the cost of water treated by packed tower aeration.

378

GAC Adsorption Treatment

GAC adsorption removal of most organic contaminants from drinking water, especially ground waters, is very good. There are a few exceptions including low molecular weight compounds such as vinyl chloride. Experiments with this chemical have shown removal of it from water to be erratic using GAC adsorption columns.

The capacity of carbon for removing a contaminant from water can be determined empirically. Generally, GAC adsorption removes the contaminant to below its detection limit until the capacity of the fixed bed adsorber is reached. The point at which the contaminant is detected in the effluent water is termed breakthrough. After breakthrough the GAC may remain in service for some time until the treatment goal is reached. Carbon is replaced at intervals of three to six months or longer in practice.

Background organics, sometimes measured as total organic carbon or TOC, can increase the amount of carbon required to treat a given volume of water. This is especially a problem in surface waters. But, since the volatile organic chemicals do not occur often above one part per billion in surface waters, this may not become a major issue. It also should be noted that empirical determination of carbon usage rates at the site takes into account the competitve effects of background naturally-occurring organics (i.e., TOC).

Once the treated water goal is reached by a GAC treatment system, the carbon must be replaced or reactivated. Small systems generally have a contract with a supplier who delivers fresh carbon and removes the spent carbon. The supplier may then reactivate the carbon for use in waste water treatment. Larger systems can reactivate the GAC on-site using heat. Fluidized bed reactivation furnaces are popular for this. This thermal reactivation process can result in the discharge of particulates and combustion products of both the fuel and the adsorbed organics to air. Experiments at Cincinnati, Ohio revealed that toxic (carcinogenic) dioxins were in the stack gases of the reactivation furnace. Afterburners typically installed with reactivation furnaces remove the dioxins and other air pollutants. These concerns are not likely to limit the applicablity of GAC adsorption as BAT for the control of organic chemical contaminants in water.

Cost Considerations

The Safe Drinking Water Act requires EPA to take cost into consideration in setting standards. The objective is to set the maximum contaminant level as close to the goal (zero for carcinogens) as is feasible taking cost into consideration. Tables 1 and 2 contain cost estimates for 99% removal of nine volatile organic chemicals using GAC and aeration. For perspective, the average cost of treated drinking water in the U.S. ranges from about one dollar to a dollar and a half per 1000 gallons. Figure 3 is a table of the cost of removing trichloroethylene to various concentrations. Notice that the rate of increase of cost does not change dramatically as the percent removal increases nor are the actual costs significantly higher than that paid for treated water today. It would not be inordinate to conclude that the cost of removing volatile organic chemicals down to the analytical quantification level is reasonable.

379

The previous paragraph discussed the system level costs of removing volatile organic chemicals. At the national level total national costs are an obvious concern. Table 5 presents a summary of the national cost as a function of the selection of maximum contaminant level. A major conclusion that may be drawn is that, as the level decreases, the total number of systems required to treat increases and consequently the cost increases. The total national cost was not the major determinant in the selection of the maximum contaminant level, but was considered in the overall analysis.

FINAL RULE

The final rule promulgating maximum contaminant levels for the nine volatile organic chemicals has not been published. The EPA may change the numbers or the methodology used in determining those numbers. The solution to the risk management problem should consider that regulations for trichloroethylene and vinyl chloride are due out shortly and that a rule for aldicarb and other pesticides is also forthcoming. But, do not restrict your response to what EPA may or may not do. In other words, you must take the Health Advisory and risk assessment/management problem data and develop your own solutions and numerical goals.

Table 1

Cost for 99 percent removal (from 500 ug/l to 5 ug/l)
of the nine VOCs using packed tower aeration in
August 1983 dollars.

Compound	Costs by System Size Category*		
	100 - 500 (0.037 mgd)	3300 - 10,000 (0.95 mgd)	100,000 - 500,000 (36.8 mgd)
Trichloroethylene			
Capital cost	69,000	264,000	4,789,000
Annual O & M cost	1,400	18,000	617,000
total cost (¢/1000 gallons) 79.0		15.5	9.4
Tetrachloroethylene			
Capital cost	67,000	252,000	4,607,000
Annual O & M cost	1,200	15,000	513,000
total cost (¢/1000 gallons) 75.0		14.2	8.4
Carbon tetrachloride			
Capital cost	66,000	249,000	4,536,000
Annual O & M cost	1,200	15,000	509,000
total cost (¢/1000 gallons) 75.0		14.0	8.3
1,2-Dichloroethane			
Capital cost	84,000	461,000	10,221,000
Annual O & M cost	2,400	37,000	1,149,000
total cost (¢/1000 gallons) 101.0		28.5	18.7
Vinyl chloride			
Capital cost	60,000	201,000	3,453,000
Annual O & M costs	900	11,000	377,000
total cost (¢/1000 gallons) 66.0		11.0	6.2
1,1-Dichloroethylene			
Capital cost	64,000	229,000	3,975,000
Annual O & M costs	1,000	13,000	428,000
total costs (¢/1000 gallons) 71.0		12.5	7.1

*Number of persons served and million gallons per day

Costs by System Size Category

Compound	100 - 500 (0.037 mgd)	3300 - 10,000 (0.95 mgd)	100,000-500,000 (36.80 mgd)
Benzene			
Capital cost	74,000	325,000	6,538,000
Annual O & M cost	1,700	23,000	781,000
total cost (¢/1000 gallons)	86.0	19.2	12.3
p-Dichlorobenzene (1000 ug/l to 750 ug/l)			
Capital cost	51,000	146,000	2,489,000
Annual O & M cost	700	8,000	283,000
total cost (¢/1000 gallons)	56.0	8.1	4.6
1,1,1-Trichloroethane (500 ug/l to 200 ug/l)			
Capital cost	52,000	150,000	2,500,000
Annual O & M costs	700	8,500	290,000
total cost (¢/1000 gallons)	57.0	8.2	4.7

TABLE 2

Cost for 99 percent removal (from 500 ug/l to 5 ug/l) of the
nine VOCs using granular activated carbon adsorption in
August 1983 dollars

	Costs by System Size Category*		
Compound	100 - 500 (0.037 mgd)	3300 - 10,000 (0.95 mgd)	100,000-500,000 (36.8 mgd)
Trichloroethylene			
Capital cost	24,000	240,000	9,000,000
Annual O & M cost	4,500	86,000	710,000
Total cost (¢/1000 gallons)	57.0	34.0	14.0
Tetrachloroethylene			
Capital cost	24,000	240,000	7,700,000
Annual O & M cost	2,800	45,000	400,000
Total cost (¢/1000 gallons)	45.0	22.0	11.0
Carbon tetrachloride			
Capital cost	24,000	240,000	9,800,000
Annual O & M cost	5,700	85,000	930,000
Total cost (¢/1000 gallons)	66.0	34.0	17.0
1,2-Dichloroethane			
Capital cost	24,000	240,000	11,000,000
Annual O & M cost	9,400	150,000	1,500,000
Total cost (¢/1000 gallons)	93.0	52.0	23.0
Vinyl chloride			
Capital cost	NA	NA	NA
Annual O & M cost	NA	NA	NA
Total cost (¢/1000 gallons)	NA	NA	NA
1,1-Dichloroethylene			
Capital cost	24,000	240,000	9,100,000
Annual O & M cost	4,600	90,000	740,000
Total cost (¢/1000 gallons)	58.0	35.0	15.0

*Number of persons served and million gallons per day

Costs by System Size Category

Compound	100 - 500 (0.037 mgd)	3300 - 10,000 (0.95 mgd)	100,000-500,000 (36.8 mgd)
Benzene			
Capital cost	24,000	236,000	17,200,000
Annual O & M cost	15,700	258,000	2,800,000
Total cost (¢/1000 gallons)	150	83.3	37.6
p-Dichlorobenzene (1000 ug/l to 750 ug/l)			
Capital cost	24,000	240,000	5,100,000
Annual O & M cost	1,900	22,000	230,000
Total cost (¢/1000 gallons)	38.0	15.0	6.9
1,1,1-Trichloroethane (500 ug/l to 200 ug/l)			
Capital cost	24,000	240,000	10,000,000
Annual O & M cost	6,600	100,000	1,100,000
Total cost (¢/1000 gallons)	73.0	38.0	18.0

Table 3: Comparsion of Various Levels of Removal of Trichloroethylene (as percent versus total costs (cent per thousand gallons)

% removed	Total Cost (cents per thousand gallons) using packed tower aeration	using GAC adsorption
50	5.9	18.5
90	8.5	22.7
99	12.0	25.3

Table 4: Summary of Impacts of the Regulatory Options for Controlling Volatile Organic Chemicals (Federal Register, November 13, 1985, p.46927)

	Regulatory Options		
	1 ug/L	5 ug/L	10 ug/L
Number of Systems Impacted............................	3,800	1,300	800
Cost of Control......................			
Total cost ($M)	1,300	280	150
Annual cost ($M)	100	21	11
Cost of Monitoring...................			
Compliance ($M)	-----	9	---
Unregulated ($M) (1445)	-----	2	---
Annual cost per Family ($)............................			
very small (25-500)	96	91	90
small (501-3300)	47	41	40
medium (3301-50k)	12	12	11
large (>50k)			
Annual Cancer Cases Avoided............................	42	32	31

Table 5: Costs Impacts of MCLs At Various Levels

MCL Opts. ug/L	Estimated # systems impacted	National cost ($ millions)		Annual cost per family per size of system (dollars per year)			
		Total capital	Annual	Very small	Small	Medium	Large
1............................	3,800	1,300	100	96	47	12	8
5............................	1,300	280	21	91	41	12	3
10...........................	800	150	11	90	42	11	1

III. BACKGROUND ON THE CONTAMINATED WATER SUPPLY SYSTEM

Existing Water System

Population served: 30,000 people

Capacity: 5.1 million gallons per day

Average Demand: 3.0 million gallons per day

Maximum Day Demand: 4.2 million gallons per day

Source:

- three wells approximately 500 feet deep
- capacity of each well is 1.8 million gallons per day
- screened between 400 - 500 feet with gravel pack
- 18" steel casing from 0 - 400 feet
- portland cement grout from 0 - 200 feet
- all wells are pumped to a common manifold which flows to the water treatment plant
- soil profile: 0 - 100 ft., sandy soil; 100 - 400 ft., sand clay mixture; 400 -500 ft., wet sand and gravel; 500 feet, bedrock

Storage: 3.5 million gallons

Treatment: Iron removal using chlorine oxidation, alum coagulation, sedimentation, and rapid pressure sand filtration. Disinfection (chlorine), fluoridation and corrosion control (lime and metallic phosphates) are also practiced.

Constructed: 1957

Mechanical/Structural Condition: Excellent

Indebtedness: None

Rates: $1.05 per thousand gallons -- commercial/industrial
$ .85 per thousand gallons -- residential

Major Employers:

printing plant (50 people)
potato farming (4000 Acres)
machinery manufacturing (20 people)
shopping center (30 people)
plastic bag manufacturer (10 people)
soda bottler (50 people)
US Air Force Base (10,000 including residents)

All of the above employers are on the town water system (except the Air Force base) and are within three miles of the the water wells. The Air Force base has its own drinking water treatment plant which is supplied by a surface water source.

Water Quality Results

parameter	WELL # 1		WELL #2		WELL#3	
	raw	treat	raw	treat	raw	treat
iron [mg/L]	3.0	0.05	2.2	0.05	2.0	0.05
pH	6.0	7.8	5.9	7.8	6.2	7.8
alkalinity [mg/L]	10	110	14	110	12	110
vinyl chloride [ug/L]	40	20	14	20	6	20
trichloroethylene [ug/L]	50	60	30	60	100	60
aldicarb (total) [ug/L]	30	30	30	30	30	30
Total Organic Carbon [mg/L]	3.0	1.0	2.1	1.0	1.0	1.0

The above analyses were reported by the State Health Department lab. Since then, repeat samples have been analyzed and the results were not found to be significantly different. The health officer wants you to notify the public immediately, but will not tell you what to say. He says that no one should use the water because it contains carcinogens and other toxic chemicals. This is not all that acceptable to the town government, since they cannot provide an alternate water supply in a short time frame.

IV. DETERMINING HUMAN EXPOSURE AND RISKS

Exposure

       In order for human health effects to occur as a result of environmental
contamination, there must be a level of exposure to the contaminant high
enough to reach the target organs in toxic concentrations. Some systems
have been designed to directly measure human exposure to potentially harmful
agents, but they are not generally available for situations like this.
Exposure to possible toxins in drinking water cannot be determined precisely
in the general population.

       In the case at hand, we have three contaminants, two of which are
volatile synthetic organic chemicals normally used in industry and one is
an agricultural pesticide. This opens up a number of possible means and
routes of exposure for various individuals. First, a number of people
might be exposed to trichloroethylene in the work place, since it is frequently
used to degrease machinery parts. Agricultural workers might be expose to
aldicarb during application to the fields. These are specialized sub-
populations which might be considered in determining the "safe" dose for
the general population. We might have to do some research to find approxi-
mations for the exposures in the work place.

       °   Should we consider occupational exposures in
           determining a "safe" level in drinking water?

       °   Which people might be receiving occupational
           exposure? (see major employers list, p. III-2)
           Why?

       Concentrating on exposure in the home, we have three major routes of
exposure: breathing, oral consumption and dermal exposure. We generally
assume that the average adult drinks two liters per day and breathes 20
cubic meters of air. Another standard assumption for volatile contaminants
is half of the exposure is due to volatilization.

       °   For which contaminants might sources of exposure
           other than drinking water be a concern? Name the
           sources. What are the routes?

       °   Would a 20% relative source contribution from
           drinking water be a satisfactory assumption
           in this case?

       °   Is there any way for the residents to mitigate
           some of the exposure? Would boiling the water
           help? How should the boiling be done?

       °   The town has a central sewer system with an activated
           sludge treatment system. The activated sludge process
           includes four to five hours of vigorous aeration of the
           waste water. What is the ultimate sink (air, water, or
           land) for each contaminant?

389

Risks

In the risk assessment case study and the risk communication video tape you learned some basic principles that now need to be applied to risk management.

° In layman terms, describe the individual and population risks incurred from various sources of exposure. Describe the fate and transport of the contaminants and the relationship of this to the human risk of disease.

° How did you calculate individual and population risks for this exercise?

° What are your target numbers for correction?

° How would you quantitate and articulate the uncertainties surrounding your risk estimates?

V. OPTIONS AVAILABLE FOR REDUCING RISK

SHORT TERM

° point-of-use carbon treatment units @ $400 per year per home

° bottled water delivered to the doorstep @ $600 per home per year

° issue a boil water order @ $ 0 per year

° do nothing @ $ 0 per year

LONG TERM

° regional water supply with the Air Force @ $500,000 per year
(this water contains an annual average concentration of 98 ug/L
of Total Trihalomethanes)

° drill new wells @ $200,000 per year (extensive studies would be
required to find an uncontaminated source)

° install point-of-entry GAC adsorption treatment units in each
home @ $1,000,000 per year

° install central GAC treatment to meet the following levels of
trichloroethylene:

> 1.0 ug/L @ 19.5¢ per thousand gallons
> 5.0 ug/L @ 19.3¢ per thousand gallons
> 25.0 ug/L @ 19.0¢ per thousand gallons

° install central packed tower aeration treatment to meet the following
levels of trichloroethylene:

> 1.0 ug/L @ 5.0¢ per thousand gallons
> 5.0 ug/L @ 2.9¢ per thousand gallons
> 25.0 ug/L @ 3.7¢ per thousand gallons

° install central packed tower aeration and GAC adsorption to meet
the following levels of trichlorehthylene and aldicarb:

> 1.0 ug/L @ 22.1¢ per thousand gallons
> 5.0 ug/L @ 20.0¢ per thousand gallons
> 10.0 ug/L @ 18.3¢ per thousand gallons

Questions
° Which short and long term option (one of each) would you you
select? Why?
° What is the total annual cost of each selected option?

° What are some possible secondary impacts of the selected options?

E.

ALDICARB

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

The Office of Drinking Water's non-regulatory Health Advisory Program provides information on health effects, analytical methodology and treatment technology that would be useful in dealing with contamination of drinking water. Health Advisories also describe concentrations of contaminants in drinking water at which adverse effects would not be anticipated to occur. A margin of safety is included to protect sensitive members of the population.

Health Advisories are not legally enforceable Federal standards. They are subject to change as new and better information becomes available. The Advisories are offered as technical guidance to assist Federal, State and local officials responsible for protection of the public health.

The Health Advisory numbers are developed from data describing non-carcinogenic end-points of toxicity. They do not incorporate quantitatively any potential carcinogenic risk from such exposure. For those chemicals which are known or probable human carcinogens according to the proposed Agency classification scheme, non-zero One-day, Ten-day and Longer-term Health Advisories may be derived, with attendant caveats. Health Advisories for lifetime exposures may not be recommended. Projected excess lifetime cancer risks are provided to give an estimate of the concentrations of the contaminant which may pose a carcinogenic risk to humans. These hypothetical estimates usually are presented as upper 95% confidence limits derived from the linearized multistage model which is considered to be unlikely to underestimate the probable true risk.

[Summary Table-to be added]

This Health Advisory (HA) is based upon information presented in the Office of Drinking Water's draft Health Effects Criteria Document (CD) for Aldicarb (U.S. EPA, 1985). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA., 22161, PB # 86-117751/AS.. The toll free number is (800) 336-4700; in Washington, D.C. area: (703) 487-4650.

II. GENERAL INFORMATION AND PROPERTIES

Synonyms: 2-methyl-2-(methylthio)propionaldehyde O-methylcarbamoyl oxime

Temik®

Use: Pesticide (nematocide, acaracide)

Properties:

CAS #	116-06-3
Chemical formula	$C_7H_{14}O_2N_2S$
Molecular weight	190.3
Physical state (room temp.)	white crystals
Melting point	100°C
Boiling point	decomposes above 100°C
Vapor pressure	0.05 torr at 20°C
Specific gravity	1.195 at 25°C
Water solubility	6 g/l (room temp.)
Taste threshold (water)	-
Odor threshold (water)	-
Odor threshold (air)	odorless to light sulfur smell

Structural formula

Occurrence

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

° Aldicarb is considered to be moderately persistent as a pesticide. Aldicarb is metabolized rapidly by plants after application to its sulfoxide and sulfone. Once in the soil, aldicarb is degraded by both aerobic and anaerobic bacteria. Aldicarb has a soil half life of 2 to 6 weeks, with residual levels found up to 6 to 12 months later. Aldicarb in pond water was reported to degrade more rapidly, with a half life of 5 to 10 days. Aldicarb is expected to hydrolyze slowly over months or years in most ground and surface waters. Aldicarb and

its sulfoxide and sulfone degradation products do not bind to soil
or sediments and have been shown to migrate extensively in soil.
Aldicarb does not bioaccumulate to any great extent.

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

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

III. PHARMACOKINETICS

Absorption

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

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

Distribution

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

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

° Aldicarb, in a 1:1 molar ratio of the parent compound to the sulfone,
administered orally to laying hens in a single dose or for 21
consecutive days resulted in similar patterns of distribution with
the liver and kidneys as the main target organs (Hicks, et al., 1972).

Residues also were present in both the yolks and whites of the eggs laid by these hens.

Metabolism

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

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

Excretion

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

° Excretion of aldicarb via the lungs as CO_2 has been demonstrated as a minor route in rats (Knaak, et al., 1966) and in the milk of cows (Dorough and Ivie, 1968).

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

IV. HEALTH EFFECTS

Humans

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

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

° In a laboratory study, four adult males orally administered aldicarb at 0.1 mg/kg experienced a variety of cholinergic symptoms including malaise, weakness in their limbs, pupil contraction and loss of photo-

reactivity, epigastric cramps, sweating, salivation, nausea, vomiting and "air hunger" (Haines, 1971). These symptoms did not occur at 0.025 or 0.05 mg/kg. Depression of cholinesterase activity occurred in a dose-dependent manner with values as low as 25% of the control value measured in two subjects dosed at 0.1 mg/kg.

Animals

Short-term Exposure

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

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

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

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

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

° Feeding studies of short duration (7 to 15 days) have been conducted by various authors using aldicarb and/or its sulfone and sulfoxide. Statistically significant decreases in cholinesterase activity were observed in rats at dosage levels of 1 mg/kg/day (the approximate LD_{50} in rats) (Nycum and Carpenter, 1970) and at 2.5 mg/kg/day in chickens (Schlinke, 1970). The latter dosage also resulted in some lethality in test animals.

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

Longer-term Exposure

° Aldicarb administered for two years in the diets of rats or dogs at dosage levels up to 0.1 mg/kg/day resulted in no significant increases in adverse effects based on a variety of toxicologic endpoints (Weil and Carpenter, 1965, 1966a). In another two-year study, levels of up to 0.3 mg/kg/day resulted in no adverse effects in rats (Weil, 1975).

° Feeding studies using aldicarb sulfoxide at 0.6 mg/kg/day for two years resulted in an increase in the mortality rates of female rats (Weil, 1975).

° Higher dosages of aldicarb sulfoxide (i.e., 0.25 to 1.0 mg/kg/day) or aldicarb sulfone (1.8 to 16.2 mg/kg/day) administered in the diets of rats for three or six months resulted in decreases in cholinesterase activity in plasma, RBCs and brain (Weil and Carpenter, 1968a,b). No increases in mortality or gross or microscopic histopathology were noted in any group, however. Data derived from the lower dosage levels of this study have been used by the World Health Organization Committee on Pesticide Residues (FAO/WHO, 1980) to derive a NOAEL of 0.125 mg/kg NOEL for aldicarb sulfoxide in the rat.

Teratogenicity/Reproductive Effects

° No teratogenic or reproductive effects have been demonstrated to result from the administration of aldicarb to rats (Weil and Carpenter, 1964,1974), rabbits (IRDC, 1983) or chickens (Proctor, et al., 1976).

° No adverse effects on milk production were observed in studies of lactating cows or rats (Dorough and Ivie, 1968; Dorough, et al., 1970).

° Statistically significant inhibition of acetylcholinesterase activity has been demonstrated in the liver, brain and blood of rat fetuses when their mothers were administered aldicarb by gastric intubation on day 18 of gestation (Cambon, et al., 1979). These changes were seen at doses of 0.001 mg/kg and above and were manifested within five minutes of the administration of 0.1 mg/kg.

Mutagenicity

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

Carcinogenicity

° Neither aldicarb nor its sulfoxide or sulfone have been demonstrated to increase significantly the incidence of tumors in mice or rats in feeding studies (Weil and Carpenter, 1965; NCI, 1979). Bioassays with aldicarb in which rats and mice were fed either 2 or 6 ppm in the diet for 103 weeks revealed no tumors that could be attributed solely to aldicarb administration (NCI, 1979). It was concluded that, under the conditions of the bioassay, technical grade (99+%) aldicarb was not carcinogenic to F344 rats or B6C3F$_1$ mice of either sex. A two-year feeding study reported by Weil and Carpenter (1965) also produced no statistically significant increase in tumors over controls when rats were administered aldicarb at equivalent doses of 0.005, 0.025, 0.05 or 0.1 mg/kg bw/day in the diet. Weil (1975) similarly reported no adverse effects in Greenacres Laboratory Controlled Flora rats fed aldicarb at 0.3 mg/kg bw/day for 2 years.

° In the only skin-painting study available to date, Weil and Carpenter (1966b) found aldicarb to be noncarcinogenic to male C3H/H3J mice under the conditions of the experiment.

° Intraperitoneally administered aldicarb did not exhibit transforming or tumorigenic activity in a host-mediated assay using pregnant hamsters and nude (athymic) mice (Quarles, et al, 1979).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories are based upon the identification of adverse health effects associated with the most sensitive and meaningful non-carcinogenic end-point of toxicity. The induction of this effect is related to a particular exposure dose over a specified period of time, most often determined from the results of an experimental animal study. Traditional risk characterization methodology for threshold toxicants is applied in HA development. The general

formula is as follows:

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

Where: NOAEL or LOAEL = No-Observed-Adverse-Effect-Level
or
Lowest-Observed-Adverse-Effect-Level
(the exposure dose in mg/kg bw)

BW = assumed body weight of protected individual in kg (10 or 70)

UF(s) = uncertainty factors, based upon quality and nature of data

___ L/day = assumed daily water consumption (1 or 2), in liters

The available data suggest that the appearance of cholinergic symptoms indicative of cholinesterase enzyme inhibition is the most sensitive indicator of the effects of exposure to aldicarb. Adverse health effects appear to be related primarily to the depression of cholinesterase activity, as no other biochemical, morphological, reproductive, mutagenic or carcinogenic effects have been reported, even after chronic dosing.

Given the nature of the primary toxicity (rapidly reversible cholinesterase inhibition) of aldicarb and its oxidative metabolites/degradation products, it is apparent that the same NOAEL can be used as the basis for the derivation of acceptable levels over virtually any duration of exposure. In addition, the Health Advisories calculated in this document are appropriate for use in circumstances in which the sulfoxide and/or sulfone may be the substance(s) present in a drinking water sample. Depending upon the analytical method applied, it may not be possible to characterize specifically the residue(s) present. By establishing Health Advisories based upon data from valid studies with the most potent of the three substances, there is greater assurance that the guidance is protective to human health.

As described above, a NOAEL of 0.125 mg/kg bw/day can be determined from the Weil and Carpenter (1968b) and Mirro, et al., (1982) studies. From this NOAEL, all HA values can be determined.

One-day Health Advisory

For the 10 kg child:

$$\text{One-day HA} = \frac{(0.125 \text{ mg/kg/day})(10 \text{ kg})}{(100)(1 \text{ L/day})} = 0.012 \text{ mg/L} \quad (12 \text{ ug/L})$$

Where:

0.125 mg/kg/day = NOAEL, based upon lack of significant decreases in cholinesterase activity in rats

10 kg = assumed weight of protected individual

100 = uncertainty factor, appropriate for use with animal NOAEL

1 L/day = assumed volume of water consumed/day by 10 kg child, in liters

Ten-day Health Advisory

Since aldicarb is metabolized and excreted rapidly (>90% in urine alone in a 24-hour period following a single dose), the One- and Ten-day HA values would not be expected to differ to any extent. Therefore, it is the Ten-day HA will the same as the One-day HA (12 ug/L).

Longer-term Health Advisory

For the 10 kg child:

$$\text{Longer-term HA} = \frac{(0.125 \text{ mg/kg/day})(10 \text{ kg})}{(100)(1 \text{ L/day})} = 0.012 \text{ mg/L } (12 \text{ ug/L})$$

Where:

0.125 mg/kg/day = NOAEL, based upon lack of significant decreases in cholinesterase activity in rats

10 kg = assumed weight of protected individual

100 = uncertainty factor, appropriate for use with animal NOAEL

1 L/day = assumed volume of water consumed/day by 10 kg child

For the 70 kg adult:

$$\text{Longer-term HA} = \frac{(0.125 \text{ mg/kg/day})(70 \text{ kg})}{(100)(2 \text{ L/day})} = 0.042 \text{ mg/L } (42 \text{ ug/L})$$

Where:

70 kg = assumed weight of protected individual

2 L/day = assumed volume of water consumed/day by 70 kg adult, in liters

(Other factors as described above for 10 kg child)

Lifetime Health Advisory

Step 1: Determination of RRfD

$$\text{RRfD*} = \frac{(0.125 \text{ mg/kg/day})}{(100)} = 0.00125 \text{ mg/kg/day}$$

Where:

$$0.125 \text{ mg/kg/day} = \text{NOAEL}$$

100   = uncertainty factor appropriate for use
          with NOAEL from animal study

* RRfd = Risk Reference Dose: estimate of daily exposure
          to the human population which appears to be
          without appreciable risk of deleterious
          non-carcinogenic effects over a lifetime of
          exposure

Step 2: Determination of Lifetime HA

$$\text{Lifetime HA} = \frac{(0.00125 \text{ mg/kg/day})(70 \text{ kg})}{(2 \text{ L/day})} = 0.042 \text{ mg/L} = 42 \text{ ug/L}$$

Where:

$$0.00125 \text{ mg/kg/day} = \text{RRfD}$$

70 kg = assumed weight of protected individual

2 L/day = assumed volume of water ingested
          per day by 70 kg adult

The Lifetime Health Advisory proposed above reflect the assumption that 100% of the exposure to aldicarb residues is via drinking water. Since aldicarb is used on food crops, the potential exists for dietary exposure also. Lacking compound-specific data on actual relative source contribution, it may be assumed that drinking water contributes 20% of an adult's daily exposure to aldicarb. The Lifetime Health Advisory for the 70 kg adult would be 9 ug/l, taking this relative source contribution into account.

Evaluation of Carcinogenic Potential

Since aldicarb has been found to be noncarcinogenic under all conditions tested, quantification of carcinogenic risk for lifetime exposures through drinking water would be inappropriate.

The International Agency for Research on Cancer (IARC) has not classified the carcinogenic potential of aldicarb.

Applying the criteria described in EPA's proposed guidelines for assessment of carcinogenic risk (U.S. EPA, 1984a), the Agency has classified aldicarb in Group E: No evidence of carcinogenicity in humans. This category is used for agents that show no evidence of carcinogenicity in at least two adequate animal tests in different species or in both epidemiologic and animal studies.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

° The National Academy of Sciences proposed an ADI of 0.001 mg/kg/day based upon the two-year feeding studies in rats and dogs (NAS, 1977). NAS reaffirmed this ADI in 1983 (NAS, 1983).

° In addition, NAS also derived a chronic suggested-no-adverse-effect-level (SNARL) of 7 ug/l, using the studies mentioned above with an uncertainty factor of 1000 (NAS, 1977). The SNARL is protective of a 70 kg adult, consuming 2 liters of water per day and for whom drinking water is assumed to contribute 20 percent of the daily exposure to aldicarb residues.

° EPA's Office of Pesticide Programs established an ADI of 0.003 mg/kg/day based upon the data from the six-month rat feeding study with aldicarb sulfoxide (U.S. EPA, 1981).

° The FAO/WHO proposed ADIs for aldicarb residues of 0-0.001 mg/kg/day in 1979 and 0-0.005 mg/kg/day in 1982.

VI. ANALYSIS

° Analysis of aldicarb is by a high performance liquid chromatographic procedure used for the determination of N-methyl carbamoyloximes and N-methylcarbamates in drinking water (Method 531. Measurement of N-methyl carbamoyloximes and N-methylcarbamates in Drinking Water by Direct Aqueous Injection HPLC with Post Column Derivatization. U.S. EPA, 1984b). In this method, the water sample is filtered and a 400 uL aliquot is injected into a reverse phase HPLC column. Separation of compounds is achieved using gradient elution chromatography. After elution from the HPLC column, the compounds are hydrolyzed with sodium hydroxide. The methylamine formed during hydrolysis is reacted with o-phthalaladehyde (OPA) to form a fluorescent derivative which is detected using a fluorescence detector. The method detection limit has been estimated to be approximately 1.3 ug/L for aldicarb.

VIII. TREATMENT

° Techniques which have been used to remove aldicarb from water are carbon adsorption and filtration. Since aldicarb is converted into aldicarb sulfoxide and sulfone, all three compounds must be considered when evaluating the efficiency of any decontamination technique.

° Granular activated carbon (GAC) has been used in two studies of aldicarb removal from contaminated water (Union Carbide, 1979; ESE, 1984). Both studies utilized home water treatment units rather than large scale water treatment systems. Union Carbide tested the Hytest Model HF-1

water softener in which the ion exchange ion was replaced with 38.5
lb Filtrasorb ® 400 (Calgon GAC). The unit was operated at a flow rate
of 3 gal/min. Water spiked with 200 ppb or 1000 ppb of a mixture of
aldicarb, aldicarb sulfoxide and aldicarb sulfone in a 10:45:45 ratio
was treated. Under these conditions, the total aldicarb residue
level was reduced by 99% to 1 ppb for the treatment of 13,500 gallons
of water with 200 ppb of residues and 41,500 gallons with 1000 ppb
total residues. No breakthrough of aldicarb occurred. When the
study was terminated, the carbon had adsorbed 9 mg aldicarb residue
per gram. This value can be compared with an equilibrium loading
value of 21 mg per gram of carbon at 16[6] determined using 200 ppb
aldicarb residues. In the second study, ESE (1984) did a field
study in Suffolk County, NY. Nineteen units using type CW 12 x 40
mesh carbon were tested. After 38 months of use, breakthrough of
aldicarb occurred to levels over 7 ug/L in eight units tested.
The range of usage values can be attributed to the fact that the
natural well samples contained a variety of adsorbable substances
in addition to aldicarb.

o Chlorination also appears to offer the potential for aldicarb
   removal (Union Carbide, 1979). The company reported that 1.0 ppm
   free chlorine caused a shift in the ratio of aldicarb, its sulfoxide and
   its sulfone so that all residues were converted to the sulfoxide within
   five minutes of chlorine exposure. Normal conversion of aldicarb to
   aldicarb sulfone did not appear to be affected. On standing, the
   sulfoxide and sulfone decomposed. The decomposition products were
   not identified. However, should these be non-toxic, then chlorination
   could be feasible as an aldicarb removal technique.

o Aeration or air stripping which is commonly used to remove synthetic
   organic chemicals is not a good technique for the removal of aldicarb
   (ESE, 1984). This is because aldicarb has a low Henry's Law Constant
   $(2.32 \times 10^{-4}$ atm).

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F.

TRICHLOROETHYLENE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

The Office of Drinking Water's non-regulatory Health Advisory Program provides information on health effects, analytical methodology and treatment technology that would be useful in dealing with contamination of drinking water. Health Advisories also describe concentrations of contaminants in drinking water at which adverse effects would not be anticipated to occur. A margin of safety is included to protect sensitive members of the population.

Health Advisories are not legally enforceable Federal standards. They are subject to change as new and better information becomes available. The Advisories are offered as technical guidance to assist Federal, State and local officials responsible for protection of the public health.

The Health Advisory numbers are developed from data describing non-carcinogenic end-points of toxicity. They do not incorporate quantitatively any potential carcinogenic risk from such exposure. For those chemicals which are known or probable human carcinogens according to the proposed Agency classification scheme, non-zero One-day, Ten-day and Longer-term Health Advisories may be derived, with attendant caveats. Health Advisories for lifetime exposures may not be recommended. Projected excess lifetime cancer risks calculated by EPA's Carcinogen Assessment Group are provided to give an estimate of the concentrations of the contaminant which may pose a carcinogenic risk to humans. These hypothetical estimates usually are presented as upper 95% confidence limits derived from the linearized multi-stage model which is considered to be unlikely to underestimate the probable true risk.

[Summary Table - to be added.]

This Health Advisory (HA) is based upon information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for Trichloroethylene (U.S. EPA, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB # 86-118106/AS, $_____ . The toll free number is (800) 336-4700; in Washington, D.C. area: (703) 437-4650.

II. GENERAL INFORMATION AND PROPERTIES

Synonyms

TCE, trichloroethene

Uses

Solvent and degreaser for metal components

Properties

CAS#	79-01-6
Formula	$Cl-HC=C-Cl_2$
Physical state	Liquid
Boiling point	86.7°C
Density at 25°C	1.4
Vapor pressure	
Water solubility	
Odor threshold (water)	0.5 mg/L (Cherkinski, 1951)
Odor threshold (air)	2.5-900 mg/m³ (van Gemert and Nettenbreijer, 1977)

Occurrence

* Trichloroethylene is a synthetic chemical with no natural sources.

* Production of trichloroethylene was 200 million lbs in 1982 (U.S. ITC, 1983).

* The major source of trichloroethylene released to the environment is from its use as a metal degreaser. Since trichloroethylene is not consumed during this use, the majority of all trichloroethylene production is released to the environment. Most of the releases occur to the atmosphere by evaporation. However, trichloroethylene which is not lost to evaporation becomes heavily contaminated with grease and oil and is disposed of by burial in landfills, dumping on the ground or into sewers. Because metal working operations are performed nationwide, trichloroethylene releases occur in all

industrialized areas. Releases of trichloroethylene during production
and other uses are relatively minor.

° Trichloroethylene released to the air is degraded in a matter of a few
   days. Trichloroethylene released to surface waters migrates to the
   atmosphere in a few days or weeks where it also degrades. Trichloro-
   ethylene which is released to the land does not degrade rapidly and
   migrates readily to ground water. Trichloroethylene remains in
   ground water for months to years. Under certain conditions, trichloro-
   ethylene in groundwater appears to degrade to dichloroethylene and
   vinyl chloride. Trichloroethylene also may be formed in ground water
   by the degradation of tetrachloroethylene (Parsons, 1984; Vogel,
   1985). Trichloroethylene, unlike other chlorinated compounds, does
   not bioaccumulate in individual animals or food chains.

• Because of the large and dispersed releases, trichloroethylene occurs
   widely in the environment. Trichloroethylene is ubiquitous in the air
   with levels in the ppt to ppb range. Trichloroethylene is a common
   contaminant in ground and surface waters with higher levels found in
   ground water. Surveys of drinking water supplies have found that 3%
   of all public systems derived from well water contain trichloroethylene
   at levels of 0.5 ug/L or higher. A small number of systems (0.04%)
   have levels higher than 100 ug/L. Public systems derived from surface
   water also have been found to contain trichloroethylene but at lower
   levels. Trichloroethylene has been reported to occur some foods in
   the ppm range.

• The major sources of exposure to trichloroethylene are from contaminated
   water and to a lesser extent air. Food is only a minor source of tri-
   chloroethylene.

III. PHARMACOKINETICS

Absorption

• Data on absorption of ingested TCE are limited. When a dose of 200
   mg/kg of ^{14}C-TCE in corn oil was administered to rats, 97% of the
   dose was recovered during 72 hours after dosing (DeKant, et al.,
   1974).

Distribution

• Doses of 0, 10, 100 or 1,000 mg TCE/kg/day administered by gavage to
   rats five days/week for six weeks (Zenick, et al., 1984). Marginal
   increases in TCE tissue levels were detected in the 10 mg/kg/day and
   100 mg/kg/day dose groups. Compared to controls, a marked increase
   in TCE levels in most tissues was observed in the highest dose group.
   TCE was distributed in all tissues examined with the highest concen-
   trations in the fat, kidney, lung, adrenals, vas deferens, epididymis,
   brain and liver.

Metabolism

* Studies indicate that TCE is metabolized to trichloroethylene oxide, trichloracetaldehyde, trichloroacetic acid, monochloroacetic acid, trichloroethanol and trichloroethanol glucuronide (U.S. EPA, 1984a).

Excretion

* Trichloroethylene and its metabolites are excreted in urine, by exhalation and, to a lesser degree, in sweat, feces and saliva (Soucek and Vlachova, 1959).

IV. HEALTH EFFECTS

Humans

Short-term Exposure

* Oral exposure of humans to 15 to 25 ml (21 to 35 g) quantities of TCE resulted in vomiting and abdominal pain, followed by transient unconsciousness (Stephans, 1945).

Longer-term Exposure

* Studies of humans exposed occupationally have shown an increase in serum transaminases, which indicates damage to the liver parenchyma (Lachnit, 1971). Quantitative exposure levels were not available.

Animals

Short-term Exposure

* The acute oral LD$_{50}$ of trichloroethylene in rats is 4.92 mg/kg (NIOSH, 1980).

Longer-term Exposure

* Rats exposed to 300 mg/m^3 (55 ppm) TCE five days/week for 14 weeks had elevated liver weights (Kimmerle and Eben, 1973).

Mutagenicity

* Trichloroethylene was mutagenic in Salmonella typhimurium and in the B. coli K-12 strain, utilizing liver microsomes for activation (Greim, et al., 1975, 1977).

Carcinogenicity

* Technical TCE (with epichlorohydrin and other compounds) was found to induce a hepatocellular carcinogenic response in mice (NCI, 1976). Under the conditions of this experiment, a carcinogenic response was not observed in rats. The "time-weighted" average doses were 549 and

411

1,097 mg/kg for both male and female rats. The time-weighted average daily doses were 1,169 and 2,339 mg/kg for male mice and 869 and 1,783 mg/kg for female mice.

- Epichlorohydrin-free trichloroethylene was reported to be carcinogenic in mice (NCI, 1980). It was not found to be carcinogenic in female

  rats. The experiment with male rats was considered to be inadequate since these rats received doses of TCE that exceeded the maximum tolerated dose.

- TCE has been shown to be carcinogenic in different strains of mice utilizing the inhalation as well as the oral route of exposure. The National Cancer Institute (1976) and the National Toxicology Program (1982) conducted two separate studies with TCE contaminated with epichlorohydrin and with TCE free of epichlorohydrin. In these studies, B6C3F$_1$ mice were used, and the results were unequivocally positive, showing liver neoplasms.

- In an inhalation study, Henschler, et al. (1980) reported dose-related malignant lymphomas in female mice (NMRI strain). However, the authors downplayed the significance of this observation, indicating that this strain of mice has a high incidence of spontaneous lymphomas.

- Fukuda, et al. (1983) found pulmonary adenocarcinomas in female ICR mice on exposure to TCE vapor.

- Henschler, et al. (1984) tested Swiss (ICR/HA) mice and reported that when the animals were gavaged with TCE in corn oil, no statistical differences were observed in the incidence of cancers. The results of this study can be questioned because the dose schedule was often interrupted even with half of the original dose. Therefore, it is very difficult to assess the exposure. A slight increase in tumors was found in all groups treated with TCE but did not approach statistical significance.

- The Van Duuren study (1979) with skin applications of TCE in ICR/HA mice does not negate the positive findings with other strains of mice and other routes of exposure.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories are based upon the identification of adverse health effects associated with the most sensitive and meaningful non-carcinogenic end-point of toxicity. The induction of this effect is related to a particular exposure dose over a specified period of time, most often determined from the results of an experimental animal study. Traditional risk characterization methodology for threshold toxicants is applied in HA development. The general formula is as follows:

$$\frac{(NOAEL \ or \ LOAEL) \ (BW)}{(UF(s)) \ (\_\_ \ L/day)} = \_\_ \ ug/L$$

Where:

NOAEL or LOAEL = No-Observed-Adverse-Effect-Level
  or
  Lowest-Observed-Adverse-Effect-Level
  (the exposure dose in mg/kg bw)

BW = assumes body weight of protected individual
  in kg (10 or 70)

UF(s) = uncertainty factors, based upon
  quality and nature of data

__ L/day = assumes daily water consumption (1 or 2) in liters

One-day and Ten-day Health Advisory

Suitable data were not available to estimate One-day and Ten-day Health Advisories.

Longer-term Health Advisory

No suitable data are available from which to calculate a Longer-term Health Advisory.

Lifetime Health Advisory

Trichloroethylene may be classified in Group B: Probable Human Carcinogen, according to EPA's proposed weight-of-evidence scheme for the classification of carcinogenic potential. Because of this, caution must exercised in making a decision on how to deal with possible lifetime exposure to this substance. The risk manager must balance this assessment of carcinogenic potential against the likelihood of occurrence of health effects related to non-carcinogenic end-points of toxicity. In order to assist the risk manager in this process, drinking water concentrations associated with estimated excess lifetime cancer risks over the range of one in ten thousand to one in a million for the 70 kg adult, drinking 2 liters of water per day, are provided in the following section. In addition, in this section, a Drinking Water Equivalent Level (DWEL) is derived. A DWEL is defined as the medium-specific (in this case, drinking water) exposure which is interpreted to be protective for non-carcinogenic end-points of toxicity over a lifetime of exposure. The DWEL is determined for the 70 kg adult, ingesting 2 liters of water per day. Also provided is an estimate of the excess cancer risk that would result if exposure were to occur at the DWEL over a lifetime.

Neither the risk estimates nor the DWEL take relative source contribution into account. The risk manager should do this on a case-by-case basis, considering the circumstances of the specific contamination incident that has occurred.

The study by Kimmerle and Eben (1973) is the most appropriate from which to derive the DWEL. This study evaluated the subacute exposure to trichloroethylene via inhalation by adult rats for some 14 weeks following exposure to 55 ppm (300 mg/m^3), five days a week. Indices of toxicity include hematological investigation, liver and renal function tests, blood glucose and organ/body weight ratios. Liver weights were shown to be elevated while other test values were not different from controls. The elevated liver weights could be interpreted to be the result of hydropic changes or fatty accumulation. The no-observed-effect level was not identified since only a single concentration was administered. From these results, a LOAEL 55 ppm (300mg/m^3) was identified using the LOAEL, the DWEL is derived as follows:

Step 1:   Determination of Total Absorbed Dose (TAD*)

$$*TAD = \frac{(300\ mg/m^3)\ (8\ m^3/day)\ (5/7)\ (0.3)}{(70\ kg\ )} = 7.35\ mg/kg/day$$

Where:

300 mg/m^3 = LOAEL

8 m^3/day = Volume of air inhaled during the exposure period

5/7   = Conversion factor for adjusting from 5 days/week exposure to a daily dose

0.3   = Ratio of the dose absorbed.

70 kg   = Assumed weight of adult

Step 2:   Determination of RRfD*

$$RRfD* = \frac{(7.35\ mg/kg/day)}{(100)\ (10)} = 0.00735\ mg/kg/day$$

Where:

7.35 mg/kg/day = TAD

100   = uncertainty factor appropriate for use with data from an animal study.

10   = uncertainty factor appropriate for use in conversion of LOAEL to NOAEL

*RRfD = Risk Reference Dose: estimate of daily exposure to the human population which appears to be without appreciable risk of deleterious non-carcinogenic effects over a lifetime of exposure.

Step 3: Determination of the DWEL

$$DWEL = \frac{(0.00735 \ mg/kg/day)(70 \ kg)}{2 \ L/day} = 0.26 \ mg/L \quad (260 \cdot ug/L)$$

Where:

   0.00735 mg/kg/day = RRfD

   70 kg   = Assumed weight of protected individual

   2 L/day = Assumed volume of water ingested by 70 kg adult

The estimated excess cancer risk associated with lifetime exposure to drinking water containing trichloroethylene at 260 ug/L is approximately 1×10^{-4}. This estimate represents the upper 90% confidence limit from extrapolations prepared by EPA's Carcinogen Assessment Group using the linearized, multistage model. The actual risk is unlikely to exceed this value, but there is considerable uncertainty as to the accuracy of risks calculated by this methodology.

Evaluation of Carcinogenic Potential

Using the improved multi-stage model, it can be estimated that water with TCE concentrations of 280 ug/L, 28 ug/L or 2.8 ug/L would increase the risk of one excess cancer per 10^4, 10^5 or 10^6 people exposed, respectively. These estimates were calculated from the 1976 NCI bioassay data, which utilized TCE contaminated with epichlorohydrin. Since then, an NCI bioassay utilizing epichlorohydrin-free TCE has become available; the data from this bioassay have been reviewed and evaluated for carcinogenicity, and epichlorohydrin-free TCE has been reported to be carcinogenic in mice.

IARC has classified trichloroethylene in Group 3.

Trichloroethylene has been classified in Group B2: Probable Human Carcinogen. This classification for carcinogenicity was determined by a technical panel of EPA's Risk Assessment Forum using the proposed EPA risk assessment guidelines for carcinogens (FR 49 (227):46294-46301).

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

* The NAS (1980) recommended One- and Seven-day SNARLS of 105 and 15 mg/L, respectively.

* The WHO (1984) recommended a drinking water guidance level of 30 ug/L based on a carcinogenic end point.

* The EPA (U.S. EPA, 1980) recommended a water quality criterion of 6.77 mg/L for effects other than cancer.

VII. ANALYSIS

- Analysis of trichloroethylene is by a purge-and-trap gas chromato-graphic procedure used for the determination of volatile organohalides in drinking water (Method 502.1. Volatile halogenated organic compounds in water by purge and trap gas chromatography, U.S. EPA, 1985a). This method calls for the bubbling of an inert gas through the sample and trapping trichloroethylene on an adsorbant material. The adsorbant material is heated to drive off the trichloroethylene onto a gas chromatographic column. This method is applicable to the measurement of trichloroethylene over a concentration range of 0.01 to 1500 ug/L. Confirmatory analysis for trichloroethylene is by mass spectrometry (Method 524.1. Volatile organic compounds in water by purge and trap gas chromatography/mass spectrometry. U.S. EPA, 1985b). The detection limit for confirmation by mass spectrometry is 0.2 ug/L.

VIII. TREATMENT

- Treatment technologies which will remove trichloroethylene (TCE) from water include granular activated carbon (GAC) adsorption, aeration and boiling.

- Dobbs and Cohen (1980) developed adsorption isotherms for several organic chemicals including TCE. It was reported that Fibrasorb® 300 carbon exhibited adsorptive capacities of 7 mg, 1.6 mg and 0.4 mg TCE/gm carbon at equilibrium concentrations of 100, 10 and 1 mg/L, respectively. USEPA-DWRD installed pilot-scale adsorption columns at different sites in New England and Pennsylvania. In New England, contaminated well water with TCE concentrations ranging from 0.4 to 177 mg/L was passed through GAC columns until a breakthrough concentration of 0.1 mg/L was achieved with empty bed contact time (EBCT) of 18 and 9 minutes, respectively (Love and Eilers, 1982). In Pennsylvania, TCE concentrations ranging from 20 to 130 mg/L were reduced to 4.5 mg/L by GAC after 2 months of continuous operation (ESE, 1985).

- TCE is amenable to aeration on the basis of its Henry's Law Constant of 550 atm (Kavanaugh, et al., 1980). In a full plant-scale (3.78 MGD) redwood slat tray aeration column, a removal efficiency of 50-60% was achieved from TCE initial concentrations of 8.3-39.5 mg/L at an air-to-water ratio of 30:1 (Hess, et al., 1981). In another full plant-scale (6.0 MGD) multiple tray aeration column study, TCE removal of 52% was achieved from 150 mg/L (Hess, et. al., 1981). A full plant-scale packed tower aeration column removed 97-99% of TCE from 1,500-2,000 mg/L contaminated groundwater at air-to-water ratio of 25:1 (ESE, 1985).

- Boiling also is effective in eliminating TCE from water on a short-term, emergency basis. Studies have shown 5 minutes of vigorous boiling will remove 95% of TCE originally present (Love and Eilers, 1982).

° Air stripping is an effective, simple and relatively inexpensive process for removing TCE and other volatile organics from water. However, use of this process then transfers the contaminant directly to the air stream. When considering use of air stripping as a treatment process, it is suggested that careful consideration be given to the overall environmental occurrence, fate, route of exposure and various other hazards associated with the chemical.

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G.

VINYL CHLORIDE

Health Advisory Draft
Office of Drinking Water
U.S. Environmental Protection Agency

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[Summary table—to be added]

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II. GENERAL INFORMATION AND PROPERTIES

Synonyms

° Monochloroethylene, chloroethene

Uses

° Vinyl chloride and polyvinyl chloride (PVC) are used as raw materials in the rubber, paper, glass and automotive industries. In addition, vinyl chloride and PVC are used in the manufacture of electrical wire insulation and cables, piping, industrial and household equipment, medical supplies, food packaging materials and building and construction products. Vinyl chloride and PVC copolymers are distributed and processed in a variety of forms, including dry resins, plastisol (dispersions in plasticizers), organosol (dispersions in plasticizers plus volatile solvent), and latex (a colloidal dispersion in water used to coat paper, fabric or leather) (U.S. EPA, 1985a).

Properties

CAS #	75-01-4
Chemical Formula	$H_2C=CHCl$
Molecular weight	62.5
Physical state	gas
Boiling point	-13.3°C
Vapor pressure	2,530 mm at 20°C
Specific gravity	0.91
Water solubility	1.1 g/L water at 28°C
Taste Threshold (water)	not available
Odor threshold (water)	not available

Structural formula	H-C=C-Cl
	     | |
	     H H

Occurrence

° Vinyl chloride is a synthetic chemical with no natural sources.

° Production of vinyl chloride was approximately 7 billion lbs in 1983
(U.S. ITC, 1983). Vinyl chloride is used consumptively and little is
released to the environment. Environmental releases will be limited
to the areas where vinyl chloride is produced and used.

° Vinyl chloride released to the air is degraded in a matter of a few
hours (U.S.EPA, 1980). Vinyl chloride released to surface waters
migrates to the atmosphere in a few hours or days where it also
degrades. Vinyl chloride which is released to the ground does not
adsorb onto soil and migrates readily to ground water. Evidence from
laboratory studies suggests that vinyl chloride in ground water may
degrade to CO_2 and Cl^- (McCarty, 1985). Vinyl chloride is expected
to remain in ground water for months to years. Vinyl chloride has
been reported to be a degradation product of trichloroethylene and
perchloroethylene in ground water (Parsons, 1984). Vinyl chloride,
unlike other chlorinated compounds, does not bioaccumulate in indi-
vidual animals or food chains.

° Vinyl chloride does not occur widely in the environment because of
its rapid degradation and limited release. Vinyl chloride is a
relatively rare contaminant in ground and surface waters with higher
levels found in ground water. The Ground Water Supply Survey of
drinking water supplies have found that less than 2% of all ground
water derived public water systems contain vinyl chloride at levels
of 1 ug/L or higher. Vinyl chloride almost always co-occurs with
trichloroethylene. Public systems derived from surface water also
have been found to contain vinyl chloride but at lower levels. No
information on the levels of vinyl chloride in food have been identi-
fied. Based upon the limited uses of vinyl chloride and its physical
chemical properties, little or no exposure is expected from food.
Vinyl chloride occurs in air in urban areas and near the sites of its
production and use. Atmospheric concentrations are in the ppt
range.

° The major source of exposure to vinyl chloride is from contaminated
water.

III. PHARMACOKINETICS

Absorption

° Vinyl chloride is absorbed rapidly in rats following ingestion and
inhalation (Withey, 1976; Duprat, et al., 1977).

Distribution

° Upon either inhalation or ingestion of ^{14}C-vinyl chloride in rats, the
greatest amount of ^{14}C activity was found in liver followed by kidney,
muscle, lung and fat (Watanabe, et al., 1976a,b). However, another
study of inhalation exposure of rats to ^{14}C-vinyl chloride showed
the highest ^{14}C activity in liver and kidney, followed by spleen and
brain (Bolt, et al., 1976).

Metabolism

° Bartsch and Montesano (1975) reported two possible metabolic pathways for vinyl chloride, one involving alcohol dehydrogenase, the other involving mixed function oxidase. Hefner, et al. (1975) concluded that the dominant pathway at lower exposure levels probably involves alcohol dehydrogenase.

° Vinyl chloride metabolism is saturable (Watanabe, et al., 1976a; Bolt, et al., 1977).

Excretion

° Rats administered vinyl chloride by ingestion or inhalation expire greater amounts of unmetabolized vinyl chloride as the dose is increased (Watanabe, et al., 1976a, b).

° Vinyl chloride metabolites are excreted mainly in the urine. In rats, urinary metabolites include N-acetyl-5-(2-hydroxyethylcysteine) and thiodiglycolic acid (Watanabe, et al., 1976a).

° Using statistical modeling, Withey and Collins (1976) concluded that, for rats, a total liquid intake containing 20 ppm vinyl chloride would be equivalent to an inhalation exposure of about 2 ppm for 24 hours.

HEALTH EFFECTS

Humans

° At high inhalation exposure levels, workers have experienced dizziness, headaches, euphoria and narcosis (U.S. EPA, 1985a).

° Symptoms of chronic inhalation exposure of workers to vinyl chloride include hepatotoxicity (Marstellar, et al. 1975), acro-osteolysis (Lilis, et al., 1975), central nervous system disturbances, pulmonary insufficiency, cardiovascular toxicity, and gastrointestinal toxicity (Selikoff and Hammond, 1975).

Animals

Short-term exposure

° Inhalation exposure to high levels of vinyl chloride can induce narcosis and death, and, to lower doses, ataxia, congestion and edema in lungs and hyperemia in liver in several species (U.S. EPA, 1985a).

Longer-term exposure

° Administration of vinyl chloride monomer to rats by gavage for 13 weeks resulted in hematologic, biochemical and organ weight effects at doses above 30 mg/kg (Feron, et al., 1975).

° Inhalation exposure of rats, guinea pigs, rabbits and dogs to 50 ppm vinyl chloride, 7 hours/day, 130 exposures in 189 days, did not induce toxicity. Rats exposed to 100 ppm, 7 hours/day for 6 months, had increased liver weights (Torkelson, et al., 1961).

Teratogenicity/Reproductive Effects

° Inhalation exposure of rats and rabbits to vinyl chloride concentrations as high as 2,500 ppm on days 6 to 15 (rats) and 6 to 18 (rabbits) of gestation and mice to vinyl chloride levels as high as 500 ppm on days 6 to 15 of gestation did not induce teratogenic effects (John, et al., 1977).

° Potential effects on reproductive capacity have not been studied.

Mutagenicity

° Chromosomal effects of vinyl chloride exposure in workers is conflicting in that positive (Ducatmann, et al., 1975; Purchase, et al., 1975) and negative (Killian, et al., 1975; Picciano, et al., 1977) results have been reported.

° Vinyl chloride is mutagenic, presumably through active metabolites in various systems including metabolically activated systems with S. typhimurium (Bartsch, et al., 1975), E. coli (Greim, et al., 1975), yeast (Loprieno, et al., 1977), germ cells of Drosophila (Verburgt and Vogel, 1977) and Chinese hamster V79 cells (Hubermann, et al., 1975).

Carcinogenicity

° Increases in the occurrence of liver angiosarcomas as well as in tumors of the brain, lung, and hematopoietic and lymphopoietic tissues have been associated with occupational exposure to vinyl chloride in humans (IARC, 1979).

° Ingestion of vinyl chloride monomer in the diet by rats at feeding levels as low as 1.7 mg/kg/day over their lifespan induced liver angiosarcomas and hepatocellular carcinomas, as well as other adverse hepatic effects (Feron, et al., 1981). Til, et al. (1983) extended the Feron, et al. (1981) work to include lower doses and did not find a significant (P<0.05) increase in carcinogenic effects at feeding levels as high as 0.13 mg/kg/day. Administration of vinyl chloride monomer by gastric intubation for at least 52 weeks resulted in carcinogenic effects in liver and other tissue sites in rats (Feron, et al., 1981; Maltoni, 1981).

° Chronic inhalation of vinyl chloride has induced cancer in liver and other tissue sites in rats and mice (Lee, et al., 1977, 1978; Maltoni, 1981).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories are based upon the identification of adverse health effects associated with the most sensitive and meaningful non-carcinogenic end-point of toxicity. The induction of this effect is related to a particular exposure dose over a specified period of time, most often determined from the results of an experimental animal study. Traditional risk characterization methodology for threshold toxicants is applied in HA development. The general formula is as follows:

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

Where:

NOAEL or LOAEL = No-Observed-Adverse-Effect-Level
                 or
                 Lowest-Observed-Adverse-Effect-Level
                 (the exposure dose in mg/kg bw)

BW   = assumed body weight of protected individual
                 in kg (10 or 70)

UF(s)   = uncertainty factors, based upon
                 quality and nature of data

__ L/day   = assumed daily water consumption (1 or 2) in liters

One-day Health Advisory

There are insufficient data for calculation of a One-day Health Advisory. The Ten-day HA is proposed as a conservative estimate for a One-day HA.

Ten-day Health Advisory

Feron, et al. (1975) reported a subchronic toxicity study in which vinyl chloride monomer (VCM) dissolved in soybean oil was administered by gavage to male and female Wistar rats, initially weighing 44 g, at doses of 30, 100 or 300 mg/kg once daily, 6 days per week for 13 weeks. Several hematological, biochemical and organ weight values were significantly (P<0.05 or less) different in both mid- and high-dose animals compared to controls. The NOAEL in this study was identified as 30 mg/kg.

The Ten-day HA, as well as the One-day HA, for a 10 kg child is calculated

as follows:

$$\text{Ten-day HA} = \frac{(30 \ \text{mg/kg/day} \ (6/7) \ (10 \ \text{kg})}{(100) \ (1 \ \text{L/day})} = 2.6 \ \text{mg/L} \ (2,600 \ \text{ug/L})$$

Where:

30 mg/kg/day   = NOAEL for subchronic toxicity from the Feron, et al. (1975) study

6/7   = expansion of 6 days/week treatment in the Feron, et al. (1975) study to 7 days/week to represent daily exposure

10 kg   = assumed weight of child

1 L/day   = assumed amount of water consumed by a child

100   = uncertainty factor for extrapolating results of animal study with a NOAEL to humans and for protection of the most sensitive members of the population.

This HA is equivalent to 2.6 mg/day or 0.26 mg/kg/day.

Longer-term Health Advisory

The Longer-term HA can be calculated from the lifetime feeding study in rats by Til, et al. (1983). Til, et al. (1983) have extended the earlier work by Feron, et al. (1981) to include lower doses with basically the same protocol used in the latter study. Carcinogenic and noncarcinogenic effects were evident with a vinyl chloride dietary level of 1.3 mg/kg/day. At dietary levels of 0.014 and 0.13 mg/kg/day, increased incidences of basophilic foci of cellular alteration in the liver of female rats were evident. However, basophilic foci by themselves are concluded not to represent an adverse effect on the liver in the absence of additional effects indicative of liver lesions such as those found in the 1.3 mg/kg/day group; and a dose-related increase in basophilic foci was not evident. Therefore, the dose of 0.13 mg/kg/day is identified as the NOAEL for noncarcinogenic effects for the Longer-term HA calculation.

Using the 0.13 mg/kg/day NOAEL from the Til, et al. (1983) study, the Longer-term HA is for a child calculated as follows:

$$\text{Longer-term HA} = \frac{(0.13 \text{ mg/kg/day}) (10 \text{ kg})}{(100) (1 \text{ L/day})} = 0.013 \text{ mg/L or } 13 \text{ ug/L}$$

Where:

0.13 mg/kg/day   = NOAEL from the Til, et al. (1983) study

10 kg   = assumed weight of child

1 L/day   = water consumption per day for a child

100   = uncertainty factor in an animal study where a NOAEL was determined.

This HA is equivalent to 13 ug/day or 1.3 ug/kg/day.

By assuming 70 kg body weight and 2 L daily water consumption, the Longer-term HA for an adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.13 \text{ mg/kg/day}) \ (70 \text{ kg})}{(100) \ (2 \text{ L/day})} = 0.046 \text{ mg/L or } 46 \text{ ug/L}$$

This HA is equivalent to 92 ug/day or 1.3 ug/kg/day.

Lifetime Health Advisory

Because vinyl chloride is classified as a human carcinogen (IARC Group 1 and EPA Group A), a Lifetime Health Advisory is not recommended.

Evaluation of Carcinogenic Potential

EPA's Carcinogen Assessment Group (CAG) recently has recalculated its excess carcinogenic risk estimates resulting from lifetime exposure to vinyl chloride through the drinking water (U.S. EPA, 1984b). CAG based its preliminary revised estimates on the Feron, et al. (1981) study. The total number of tumors, considering tumors of the lung and liver, in rats exposed through the diet was used to calculate the excess cancer risk. They calculated that consuming 2 liters of water per day with vinyl chloride concentration of 1.5 ug/L, 0.15 ug/L and 0.015 ug/L would increase the risk of one excess cancer per 10,000 (10^{-4}), 100,000 (10^{-5}) or 1,000,000 (10^{-6}) people exposed, respectively, per lifetime. The CAG is presently reassessing the cancer risk estimate based on the Feron, et al. (1981) study by taking into account the more recent data by Til, et al. (1983) which, as described previously, is an extension of the earlier Feron, et al. (1981) work to include lower doses.

The IARC (1979) has concluded that the evidence is sufficient to classify vinyl chloride as a human carcinogen in its Category 1.

Applying the criteria described in EPA's proposed guidelines for assessment of carcinogenic risk (U.S. EPA, 1984a), vinyl chloride may be classified in Group A: Human carcinogen. This category is for agents for which there is sufficient evidence to support the causal association between exposure to the agents and cancer.

VI. OTHER CRITERIA, GUIDANCE, AND STANDARDS

 ° The National Academy of Sciences (NAS, 1977) estimated a 10^{-6} risk from lifetime exposure to 1 ug vinyl chloride/L drinking water with the 95% upper limit of the multistage model and the lifetime ingestion study in rats by Maltoni, et al. (1981).

 ° In June, 1984, EPA proposed a Recommended Maximum Contaminant Level (RMCL) of zero for vinyl chloride in drinking water (U.S. EPA, 1984b).

° Ambient water quality critera (U.S. EPA, 1980) are 20, 2 and 0.2 ug/L for risks of 10^{-5}, 10^{-6}, and 10^{-7}, respectively, assuming consumption of 2 liters of water and 6.5 grams of contaminated fish per day by a 70 kg adult.

° A workplace standard of 1 ppm (time-weighted average) was set by OSHA in 1974, as mentioned in U.S. EPA (1980).

VII. ANALYSIS

° Analysis of vinyl chloride is by a purge and trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water (Method 502.1. Volatile halogenated organic compounds in water by purge and trap gas chromatography. U.S. EPA, 1985b). This method calls for the bubbling of an inert gas through a sample of water and trapping the purged vinyl chloride on an adsorbant material. The adsorbant material is heated to drive off the vinyl chloride onto a gas chromatographic column. This method is applicable to the measurement of vinyl chloride over a concentration range of 0.06 to 1500 ug/L. Confirmatory analysis for vinyl chloride is by mass spectrometry (Method 524.1. Volatile organic compounds in water by purge and trap gas chromatography/mass spectrometry. U.S. EPA, 1985c). The detection limit for confirmation by mass spectrometry is 0.3 ug/L.

VIII. TREATMENT

° The value of the Henry's Law Constant for vinyl chloride (6.4 atm-m^3/mole) suggests aeration as a potential removal technique for vinyl chloride in water (ESE,1984). Removals of up to 99.27% were achieved at 9°C using a pilot packed tower aerator. In similar studies, vinyl chloride was removed from ground water using a spray aeration system with total VOC concentration was 100 to 200 ug/l (ESE, 1984). Greater than 99.9% VOC removal was obtained using a four-stage aeration system; each stage employed 20 shower heads with a pressure drop of approximately 10 pounds per square inch. In-well aeration has also demonstrated up to 97% removal of vinyl chloride using an air-lift pump. However, practical considerations are likely to limit the application of this (Miltner, 1984).

° The concentration of vinyl chloride in southern Florida ground water declined by 25% to 52% following passage through lime softening basins and filters (Wood and DeMarco, 1980). Since vinyl chloride is a highly volatile compound, probably volatilized during treatment (ESE, 1984).

° Adsorption techniques have been less successful than aeration in removing vinyl chloride from water. In a pilot study, water from a ground water treatment plant was passed through a series of four 30-inch granular activated carbon (Filtrasorb 400) columns (Wood and DeMarco, 1980; Symons, 1978); the empty bed contact time was approximately six minutes per column. Influent vinyl choride concentrations

ranged from below detection to 19 mg/l; erratic removal was reported. To maintain effluent concentrations below 0.5 mg/l, the estimated column capacity to breakthrough was 810, 1250, 2760 and 2050 bed volumes for empty bed contact times of 6, 12, 19 and 25 minutes, respectively. In addition, the estimated service life of the activated carbon was low. Similarly, poor removal of vinyl chloride was achieved using an experimental synthetic resin, Ambersorb XE-340, (Symons, 1978).

° Treatment technologies for the removal of vinyl chloride from water have not been extensively evaluated except on an experimental level. Available information suggests aeration merits further investigation. Selection of individual or combinations of technologies to achieve vinyl chloride removal must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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PART V

RISK COMMUNICATION

Outline for Videotape

Part IV - Risk Communication

A. Media Basics

Media Coverage - Advantages

o   Quick dissemination of information to public

o   Allays unfounded fears

o   Inspires confidence

Media Coverage - Disadvantages

o   Shallowness

- Tight deadlines
- Stories must be brief
- Reporters are generalists

o   Sensationalism

- News stories required daily but true sensational stories don't happen daily
- Public interest in what went wrong · not what went right

o   Subjectivity

Coping With the Disadvantages of Media Coverage

o   Shallowness

o   Sensationalism

o   Subjectivity

o   Educate reporter

o   Know and present facts

o   Appeal to values

B. Rules For Dealing With the Media

No such thing as "Off the record"

Assume microphones always on

Plan ahead

- o   Primary and backup spokesperson

- o   Inform media and government who spokesperson is   how to contact

- o   Telephone operators informed how to reach spokesperson

- o   Establish information gathering teams to report information to spokesperson

- o   Establish contingency press area with telephones and back up communications equipment

Develop ability to take control of interview

C. Controlling the Interview

Winning at confrontation

o   Rules of the game

o   Crisis communications exercise 1

You have been thrown into the middle of a hot controversy about contamination of drinking water supplies. During a public meeting, which was attended by organized protesters and the media, a woman runs up to you, pokes her finger into your chest, and calls you "not human, robot."

Evaluate the pros and cons of these various ways of dealing with her outburst:

A)   Walk out with as much dignity as you posses and issue a statement later refuting her charges.

PRO: CON:

B)   Ask the police to remove her and other hecklers from the hall.

PRO: CON:

C)   Remain silent until she calms down and then try to avoid saying anything that might agitate the audience.

PRO: CON:

439

D) Grab the microphone, ask for a chance to respond and emphatically disagree with her.

PRO: CON:

o   Guidelines for success

Dealing with fear

o   The problem

o   Crisis Communication Exercise II

After the train derailed and spilled a large quantity of chemicals, you are in charge of the cleanup. The residents don't trust the railroad and believe it is understating the potential long-term danger to drinking water supplies. Evaluate each of the following as a possible first action on your part:

A)   Hold a joint news conference with the railroad spokesman to refute the charges.

PRO: CON:

B)   Issue a statement announcing a study to ascertain the facts.

PRO: CON:

C)   Meet with residents at City Hall to hear their complaints and fill tem in on the cleanup.

PRO: CON:

D) Accelerate efforts to contain the spill and pump the liquid into tanks.

PRO: CON:

o   Guidelines for success

D. Disclosing Information

General

Ground Rules

Crisis Communications Exercise III

You are an official of a water district experiencing a prolonged drought. A
newspaper reporter calls and asks if it is true that a major industrial plant is
using water at the same rate as before the drought, despite official requests for
conservation. His information is correct. Analyze the pros and cons of each of the
following ways of answering his question.

A) Tell him to call the manufacturer. Giving out such information about
users violates privacy rights.

PRO: CON:

B) Acknowledge it's true but warn that if water usage by this industry is
cut, the budget will go in the red and the rates will go up for everyone.

PRO: CON:

C) Tell him you will seek an audit and get back to him (and give him the
results after the drought is over).

PRO: CON:

442

D) Acknowledge it's true but explain that the manufacturing process is such that there can be little variation in water consumed in the process as long as the plant is operating.

PRO: CON:

Guidelines for success

E. Conclusions and Checklist

General Risk Perception

o   The problem of involuntary risks

o   Communication Exercise IV

Assume that a volatile chemical is detected in the drinking water that your scientific experts say has about the same chance of causing cancer as saccharin. After the story is leaked to the press you appear at a town meeting. Analyze these various responses:

A) Asked "Is the water safe to drink?" you pick up a glass and chug a lug it, saying, "Safe enough for me."

PRO: CON:

B)   Tell them that it is unlikely that anyone could drink enough water every day over his/her lifetime for exposure to be a significant risk for cancer.

PRO   CON:

C)   Cite scientific data that someone who drank one glass of town water per day for 70 years would face a cancer risk of 6.4 in 10,000.

PRO: CON:

o   Guidelines for success

Crisis Communication Checklist

1. BE PREPARED. REVIEW THE FACTS.

2. BE HONEST. TELL THE TRUTH.

3. ANTICIPATE LIKELY QUESTIONS.

4. CONSIDER WHAT THE AUDIENCE IS INTERESTED IN KNOWING.

5. DECIDE WHAT YOU WANT TO SAY.

6. CONSIDER IF THERE ARE THINGS YOU DON'T WANT TO DISCUSS.

7. COMPOSE CONCISE, ACCURATE ANSWERS.

8. AVOID JARGON.

9. DON'T FLY BY THE SEAT OF YOUR PANTS, YOU MIGHT CRASH.

10. IF YOU DON'T KNOW THE ANSWER TO A QUESTION, DON'T GUESS.

11. STAY CALM, DO NOT LOSE YOUR COOL.

12. SPEAK UP, DO NOT MUMBLE.

13. BE ASSERTIVE, NOT ARROGANT.

14. DO NOT FIGHT WITH REPORTERS, BYSTANDERS, ACTIVISTS.

15. DO NOT FUDGE.

16. DO NOT SHOW FRIGHT. RELAX, BREATHE DEEPLY.

17. AVOID FLIGHT. DON'T TRY TO RUN AWAY.

18. COUNTER FALSE ASSUMPTIONS IN QUESTIONS.

19. WHEN FINISHED, STOP. IT IS HARDER TO PUT ONE'S FOOT IN ONE'S MOUTH WHEN IT IS SHUT.

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THE DOZEN MOST COMMON MISTAKES IN CRISIS COMMUNICATIONS
By Ford Rowan

The first mistake most managers make is failing to prepare for a worst case scenario. Perhaps it's human nature to avoid the unthinkable. But the single most important thing that can be done to prevent a catastrophe is to prepare for it.

The second mistake most managers make is to underestimate the importance of the media at the onset of a crisis. The dissemination of information is crucial and the presence of reporters and photographers is automatic at most serious emergencies. If the press is an unwelcome guest, it returns the cool reception by heating up the rhetoric.

The third mistake is to fail to understand the needs of the press for regular updates. Deadlines come often in this day of instant-eyes and minicams. Failing to provide concise factual updates can result in wild speculation.

The fourth mistake is the failure to establish a communications command center where information can be coordinated. Reporters will be wandering all over the place, talking with uninformed bystanders. Communications must be coordinated to assure accurate information.

The fifth mistake is to fail to take charge. The spokesperson must be a leader. His role is not just to answer questions but to disseminate information.

The sixth mistake is to fail to anticipate likely questions. The old standards   what, when, where, who, why and how   can be expected. Remember, people want to know, "Is it safe now?"

The seventh mistake is to be lured into answering hypothetical questions. Avoid "what ifs," they can be scary. When asked to predict, stick to the facts and make projections · if any · based on what is known.

The eighth mistake occurs when a spokesperson inadvertently uses an emotionally charged word or sensational phrase in response to a question. Don't contribute to hype.

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

The tenth mistake is to try to stonewall if things get worse, to fudge the facts if the situation begins to deteriorate, or to compound the confusion as fatigue sets in. Credibility is at stake; preserve it with candor.

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

The twelfth mistake is to fail to learn from mistakes. Life is full of trial and error. Put the hard earned knowledge to work to prevent future crises.

Seminar Evaluation

ASSESSMENT AND MANAGEMENT OF DRINKING WATER CONTAMINATION

Please fill in Name of City where seminar is being held:_____

Attendee's Profile - Organization You Represent (Please Mark with an "X")

_____ Municipal/Local Agency   _____ Consulting Engineer
                                                or Scientist
_____ State Agency   _____ Federal Agency

                                      _____ Other

Presentations

Please evaluate each presentation using the following scale as applicable:

1 = Excellent 2 = Good 3 = Satisfactory 4 = Marginal 5 = Unsatisfactory

Topic	Content	Speaker Effectiveness	Audio/Visual Material	Question and Answer Period
Regional update (if applicable)	_____	_____	_____	_____
Introduction to Risk Assessment and Management Problems	_____	_____	_____	_____
Principles of Toxicology	_____	_____	_____	_____
Absorption, Distribution, Excretion and Metabolism	_____	_____	_____	_____
Tox approaches to developing Natl. DW Standards	_____	_____	_____	_____
ODW Health Advisory Program	_____	_____	_____	_____
Toxicology of Inorganics, Pesticides, Solvents and Vapors	_____	_____	_____	_____

Topic	Content	Speaker Effectiveness	Audio/Visual Material	Question and Answer period
Principles of Carcinogenicity	_____	_____	_____	_____
Risk Assessment Principles	_____	_____	_____	_____
Risk Assessment Case Study	_____	_____	_____	_____
Radionuclides Lecture	_____	_____	_____	_____
Overview of Treatment as applied to Risk Management	_____	_____	_____	_____
Inorganics Treatment	_____	_____	_____	_____
Organics Treatment	_____	_____	_____	_____
Risk Communication	_____	_____	_____	_____
Risk Management Case Study	_____	_____	_____	_____

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