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Environmental Protection
Agency

Office of Drinking
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Washington DC 20460

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Technology Transfer

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EPA

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 you, but it is not our intention that this person will lecture. It is expected that each person take part in the solutions of the problems.

It is hoped that by the closing of this workshop, each participant will be able to better handle similar problems occurring in that participant's own Region, State or locality and that the procedures laid out in this workshop will improve the quality of performance on the job.

WORKSHOP ON RISK ASSESSMENT AND MANAGEMENT OF DRINKING WATER CONTAMINATION

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PART I

UNDERSTANDING EPA'S DRINKING WATER HEALTH ADVISORIES

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EPA's DRINKING WATER HEALTH ADVISORY PROGRAM*

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ABSTRACT

The Office of Drinking Water's non-regulatory Health Advisory Program provides technical guidance 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.

The Health Advisories are developed from data describing non-carcinogenic end-points of toxicity. For those chemicals which are known or probable human carcinogens according to the proposed Agency classification scheme, non-zero One-day, Ten-day, Longer-term Advisories may be derived, with attendant caveats. Advisories for lifetime exposure 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.

* Presented at the 25th Anniversary Meeting of the Society of Toxicology. The Toxicologist 6(1):280 (Abstract # 1124). March, 1986.

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

- Establish comprehensive Health Advisories Registry (Computer-based)
- Prepare new and revised Health Advisories for about 50 contaminants (FY85)
- Develop new Health Advisories for about 60 National Pesticide Survey analytes (FY86)
- Develop new Health Advisories for about 50 unregulated volatile synthetic organic chemicals under Section 1445 (FY86)
- Institute new procedures to assure timely responses to emergency situations and requests for information (FY85)
- 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
- 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 (Pilot in FY86; Deliver in FY87)

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 non-carcinogenic 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^{-4} 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

PROPOSED EPA SCHEME FOR CATEGORIZATION OF EVIDENCE OF CARCINOGENICITY

Group A: Human Carcinogen

Sufficient evidence in epidemiologic studies to support causal association between exposure and cancer

Group B: Probable Human Carcinogen

Almost sufficient to inadequate evidence in epidemiologic studies
Sufficient evidence from animal studies

Group C: Possible Human Carcinogen

Absence of data in humans
Limited evidence from animal studies

Group D: Not Classified

Inadequate animal evidence

Group E: No Evidence of Carcinogenicity for Humans

No evidence in multiple studies

ODW HEALTH ADVISORY (HA) CONTENT

I. General Introduction

II. General Information and Properties

- Synonyms
- Uses
- Properties
- Sources of Exposure
- Environmental Fate

III. Pharmacokinetics

- Absorption
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IV. Health Effects

- Humans
- Animals
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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, Guidances 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 (90d) to one year
  - Lifetime HA: Chronic
    - Subchronic (with added uncertainty factor)

- Route of Administration
  - Oral: Drinking water, Gavage, Diet
  - Inhalation
  - Subcutaneous or intraperitoneal (on a case-by-case basis)

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

DEFINITION OF ADI/RRfD

ADI = Acceptable Daily Intake

RRfD = Risk Reference Dose

The daily exposure level, which during the entire lifetime of a human, appears to be without appreciable risk on the basis of all facts known at the time (modified from Paynter, et al., 1975)

The ADI/RRfD is expressed in mg/kg bw/day

"THE MATH"

OLD METHOD:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{SF(s)}} = \text{Dose in mg/kg bw/day}$$

NEW METHOD:

$$\text{RRfD} = \frac{\text{NOAEL}}{\text{UF(s)}} = \text{Dose in mg/kg bw/day}$$

THE "DWEL"

Definition

Drinking Water Equivalent Level: Estimated exposure (in 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

SUBSTANCES FOR WHICH HEALTH ADVISORIES ARE BEING DRAFTED IN FY 86

ANALYTES FOR THE NATIONAL PESTICIDE SURVEY

Acifluorfen
Ametryn
Ammonium Sulfamate
Baygon
Bentazon
Bromacil
Butylate
Carbaryl
Carboxin
Chloramben
Chlorothalonil
Cyanazine
Cycloate
Dalapon
DCPA/Dacthal
Diazinon
Dicamba
Dieldrin
Dimethipin/Harvade
Dimethrin
Dinoseb
Diphenamid
Disulfoton
Diuron
Fenamiphos
Fluometuron
Fonofos
Hexazinone
Maleic Hydrazide
MCPA
Methomyl
Methyl Parathion
Metolachlor
Metribuzin
Nabam
Oxamyl
Paraquat
PCNB
Picloram
Prometone
Pronamide
Propazine
Propham
Treflan
Triallate
2, 4, 5-T
Tebuthiuron
Terbacil

UNREGULATED VOCs UNDER SECTION 1445

Chloromethane
Bromomethane
Bromochloromethane
1, 2, 3-Trichloropropane
1, 2, 3-Trichlorobenzene
n-Propylbenzene
1, 1, 1, 2-Tetrachloroethane
Chloroethane
1, 1, 2-Trichloroethane
Pentachloroethane
bis-2-Chloroisopropyl ether
sec-Dichloropropane
Chloroform
Bromodichloromethane
Chlorodibromomethane
Bromoform
1, 2, 4-Trichlorobenzene
Fluorotrichloromethane
Dichlorodifluoromethane
1, 2, 4-Trimethylbenzene
n-Butylbenzene
Naphthalene
Hexachlorobutadiene
o-Chlorotoluene
p-Chlorotoluene
1, 3, 5-Trimethylbenzene
p-Cymene
1, 1-Dichloropropane
iso-Propylbenzene
tert-Butylbenzene
sec-Butylbenzene
Bromobenzene
Dibromomethane
1, 1-Dichloroethane
1, 1, 2, 2-Tetrachloroethane
1, 3-Dichloropropane

FY 85 Draft Health Advisories (* NA = Not appropriate)

Chemical	One-day HA (ug/L)	Ten-day HA (ug/L)	Longer-term HA (ug/L)		Lifetime HA or DWEL at 100% (note which) (ug/L)	Lifetime HA with RSC (ug/L)	Risk at 10^{-6} (ug/L)	EPA Carcinogen Group
			10 kg	70 kg				
Acrylamide	1500	300	20	70	DWEL = 7	NA*	0.01	B
Alachlor	15000	15000	NA	NA	NA	NA	0.15	B
Aldicarb	12	12	12	42	42	9 (20%)	NA	E
Arsenic	50	50	50	50	50	50	200	A
Barium	-	-	-	—	1800	1500 (80%)	NA	D
Benzene	233	233	NA	NA	NA	NA	0.35	A
Cadmium	43	8	5	18	18	5 (25%)	NA	B1/D
Carbofuran	50	50	50	180	180	36 (20%)	NA	E
Carbon Tet.	4000	160	71	250	DWEL= 25	NA	0.3	B
Chlordane	63	63	-	-	DWEL = 30	NA	0.0218	B2
Chlorobenzene	1800	1800	9000	30000	3150	600 (20%)	NA	C
Chromium	1400	1400	240	840	170	120 (71%)	NA	A/D
Cyanide	220	220	220	750	750	750 (100%)	NA	D
2,4-D	1100	300	-	-	350	70 (20%)	NA	D
DBCP	200	50	NA	NA	NA	NA	0.025	B
o-/m-Dichlorobenzene	8930	8930	8930	31250	3125	620 (20%)	NA	D
p-Dichlorobenzene	10700	10700	10700	37500	3750	750 (20%)	NA	D
1,2-Dichloroethane	740	740	740	2600	NA	NA	0.95	B
1,1-Dichloro-ethylene	1000	1000	1000	3500	350	70 (20%)	0.24	C

FY 85 Draft Health Advisories

Chemical	One-day HA (ug/L)	Ten-day HA (ug/L)	Longer-term HA (ug/L)		Lifetime HA or DWEL at 100% (note which) (ug/L)	Lifetime HA with RSC (ug/L)	Risk at 10^{-6} (ug/L)	EPA Carcinogen Group
			10 kg	70 kg				
Cis-1,2-Dichloroethylene	4000	1000	1000	3500	350	70 (20%)	NA	D
Trans-1,2-Dichloroethylene	2720	2720	1000	3500	350	70 (20%)	NA	D
Dichloromethane	13300	1500	-	-	1750	350 (20%)	50	B
1,2-Dichloropropane	-	90	-	-	-	-	0.56	C
p-Dioxane	5680	568	-	-	-	-	?	ND*
Dioxin	1×10^{-3}	1×10^{-4}	1×10^{-5}	3.5×10^{-5}	DWEL = 1×10^{-5}	NA	2.2×10^{-7}	B
EDB	8	8	NA	NA	NA	NA	0.0005	B
Endrin	20	5	4.5	16	1.6	0.32 (20%)	NA	E
Epichlorohydrin	140	140	76	76	DWEL = 76	NA	3.5	B
Ethylbenzene	21000	2100	-	-	3400	680 (20%)	NA	D
Ethylene glycol	19000	5500	5500	19250	-	-	NA	D
Heptachlor	10	10	-	-	DWEL = 2.6	NA	0.0104	B2
Heptachlor epoxide	-	-	-	-	DWEL = 1	NA	0.0006	B2
Hexachlorobenzene	50	50	50	175	DWEL = 28	NA	0.02	B
n-Hexane	13000	4000	4000	14000	-	NA	NA	D
Lead	NA	NA	20 ug/day	20 ug/day	20 ug/day	NA	0.031	B2
Lindane	1200	1200	33	120	10	2 (20%)	0.0265	B2/C
Mercury	-	-	-	-	5.5	3 (55%)	NA	D
Methoxychlor	6400	2000	-	-	1700	340 (20%)	NA	D

Chemical	One-day HA (ug/L)	Ten-day HA (ug/L)	Longer-term HA (ug/L)		Lifetime HA or DWEL at 100% (note which) (ug/L)	Lifetime HA with RSC (ug/L)	Risk at 10^{-6} (ug/L)	EPA Carcinogen Group
			10 kg	70 kg				
Methyl ethyl ketone	75000	7500	2500	8600	860	172 (20%)	NA	D
Nickel	-	1000	-	-	350	150 (43%)	NA	B/D
Nitrate	10 mg/l- 4 kg 111 mg/L-Other	10 mg/L-4 kg 111 mg/L-Other	-	-	10 mg/L	10 mg/L(100%)	NA	D
Nitrite	1 mg/L- 4 kg 11 mg/L-Other	1 mg/L- 4 kg 11 mg/L-Other			1 mg/L	1 mg/L (100%)	NA	D
Oxamyl	350	350	-	-	810	160 (20%)	NA	E
PCBs	-	-	-	-	-	-	-	B
Pentachlorophenol	1000	300	300	1050	1050	220 (20%)	NA	D
Styrene	27000	20000	20000	70000	7000	1400 (20%)	1.4×10^{-2}	C
Tetrachloro-ethylene	-	34000	1940	6800	DWEL = 680	NA	0.7	B2
Toluene	18000	6000	-	-	10100	2000 (20%)	NA	D
Toxaphene	500	80	-	-	DWEL = 112		0.031	B2
2,4,5-TP	(200)	200	-	-	260	52 (20%)	NA	D
1,1,1-Trichloro-ethane	140000	35000	35000	125000	1000	200 (20%)	16.8 (NAS) 22 (CAG)	D
Trichloro-ethylene	-	-	-	-	DWEL = 260	NA	2.8	B2
Vinyl chloride	2600	2600	13	46	NA	NA	0.015	A
Xylenes	12000	7800	7800	27300	2200	440 (20%)	NA	D

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PART I-B-1 HEALTH ADVISORY #1

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 manufacturing and field application settings.

Distribution

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

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

° Aldicarb, in a 1:1 molar ratio of the parent compound to 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:

$$\frac{\text{(NOAEL or LOAEL) (BW)}}{\text{(UF(s)) (\_\_L/day)}} = \text{\_\_\_ ug/L}$$

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:

$$\text{Longer-term HA} = \frac{(0.125 \text{ mg/kg/day})(10 \text{ kg})}{(100)(1 \text{ L/day})} = 0.012 \text{ mg/L (12 ug/L)}$$

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:

$$\text{Longer-term HA} = \frac{(0.125 \text{ mg/kg/day})(70 \text{ kg})}{(100)(2 \text{ L/day})} = 0.042 \text{ mg/L} \quad (42 \text{ ug/L})$$

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

$$\text{RRfD}^* = \frac{(0.125 \text{ mg/kg/day})}{(100)} \equiv 0.00125 \text{ mg/kg/day}$$

Where:

0.125 mg/kg/day = 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 mg/kg/day = 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.

° 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.

° 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 (2.32×10^{-4} atm).

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September 30, 1985

PART I-C-1 HEALTH ADVISORY #2

VINYL CHLORIDE

Health Advisory Draft
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 vinyl chloride (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 # 86-118320/AS. The toll free number is (800) 336-4700; in Washington, D.C. area: (703) 487-4650.

II. GENERAL INFORMATION AND PROPERTIES

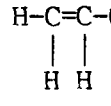
Synonyms

° 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	

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 individual animals or food chains.

- Vinyl chloride does not occur widely in the environment because of its rapid degradation and limited release. Vinyl chloride is a relatively rare contaminant in ground and surface waters with higher levels found 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 identified. Based upon the limited uses of vinyl chloride and its physical chemical properties, little or no exposure is expected from food. Vinyl chloride occurs in air in urban areas and near the sites of its production and use. Atmospheric concentrations are in the ppt range.

- 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 II

RISK ASSESSMENT

Part IIA

Principles of Toxicology

General Principles of Toxicology

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. Specialized Areas of Toxicology

A. Forensic Toxicology: A hybrid of analytical chemistry and fundamental toxicologic principles. It is concerned primarily with the medicolegal aspects of the harmful effects of chemicals on man and animals.

B. Clinical Toxicology: An area concerned with diseases caused by, or uniquely associated with toxic substances. Efforts are directed at treating patients poisoned with drugs or other chemicals and at development of new techniques to treat these intoxications.

C. Environmental Toxicology: Often used to designate evaluations made in the interest of man but dealing with compounds in the "environment."

III. 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

IV. 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

V. Chemical Exposure

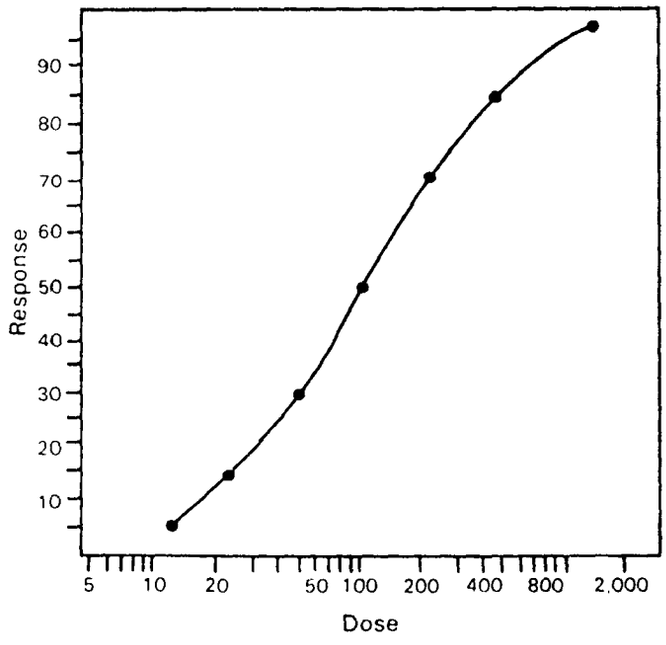
A. Acute: single

B. Subacute: less than 1 month

C. Subchronic: 1-3 months

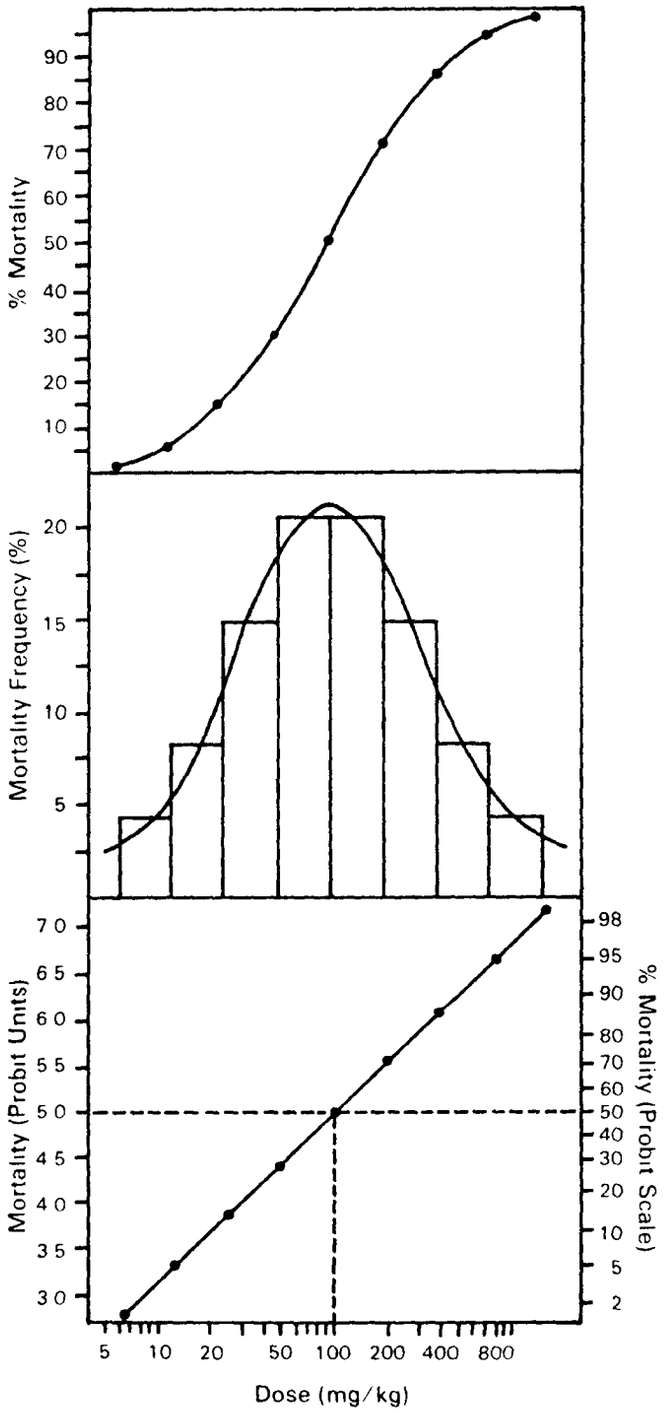
D. Chronic: more than 3 months

VI. Dose-Response



hypersusceptible
resistant

VII. Conversion of Sigmoid Dose-Response Curve to Straight Line



± 1 SD = 68.3%
± 2 SD = 95.5%
± 3 SD = 99.7%

%	NED	Probit
0.1	-3	2
2.3	-2	3
15.9	-1	4
50	0	5
84.1	+1	6
97.7	+2	7
99.9	+3	8

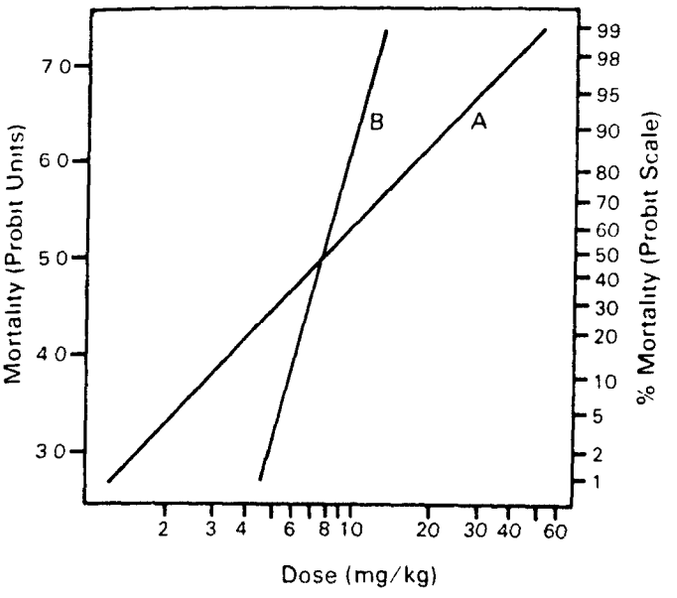
VIII. Poison: Any Chemical Capable of Producing a Deleterious Response in a Biologic System, Seriously Injuring Function or Producing Death

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

IX. 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	
TDDD	0.001	
Botulinus toxin	0.00001	

X. Slope of the Dose-Response

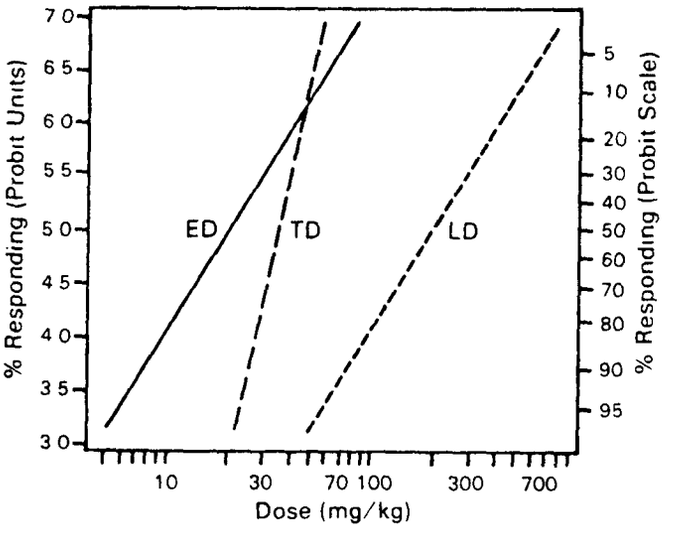


XI. Use of Dose-Response for Effects other than Death

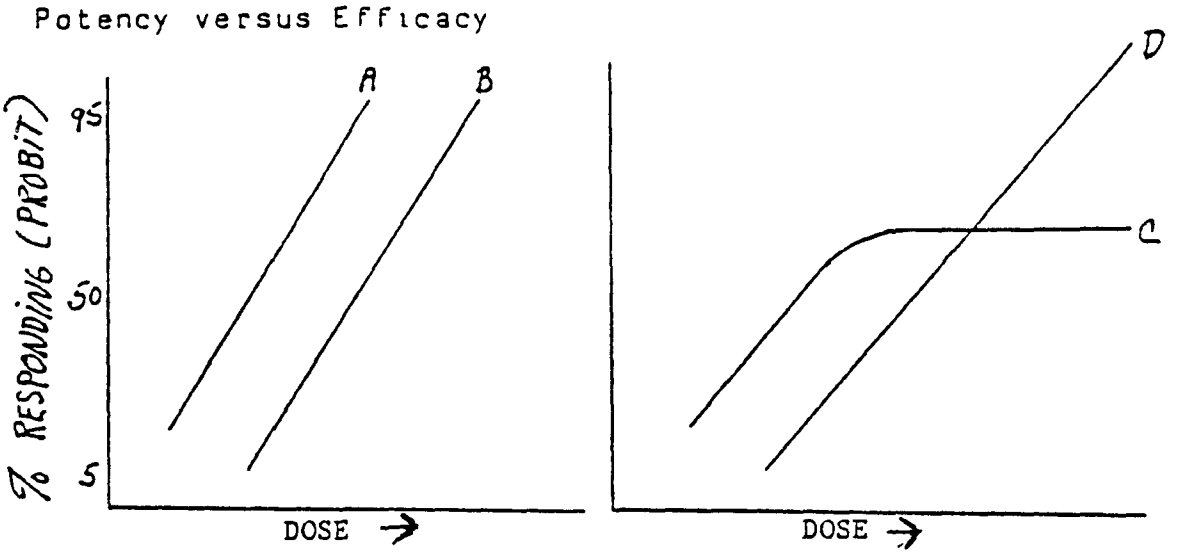
A. Liver injury

B. Cancer

C. Etc.



XII. Potency versus Efficacy



A is more potent than B: Less is required to produce the response

D is more effective than C: A higher percentage response

XIII. Therapeutic Index and Margin of Safety

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

B. Margin of safety = $\frac{\text{no observed effect level (NOEL)}}{\text{accepted daily intake (ADI)}}$

XIV. 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

XV. 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)

XVI. 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 - than 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 1,2,4 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

(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) 2 areas with intact skin and 2 with abraided skin

(5) covered by gauze and then plastic

(6) Chemical in contact with skin for 24 hrs

(7) 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. Buehler 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 consumption

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, jejunum, 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 over 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

XVII. Use of Toxicity Data in Regulations

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

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

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

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

B. Risk vs Safety

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

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

3. Estimated risks

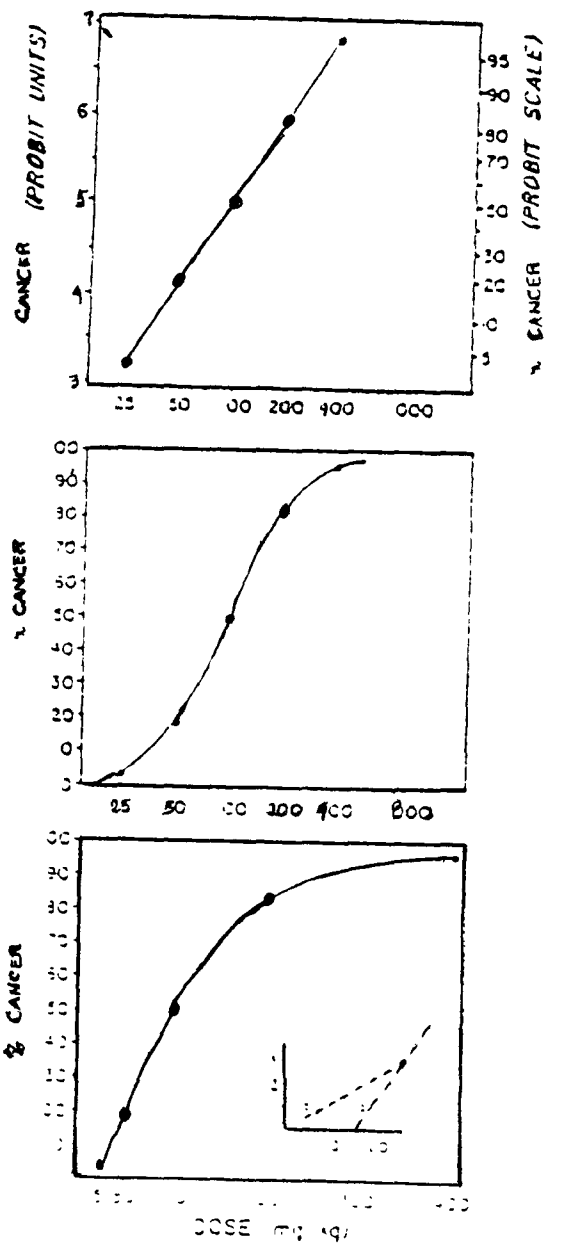
   a. 1/4000: Automobile accident
   b. 1/2,000,000: Lightning
   c. 1/5,000,000,000: Nuclear reactor accident

4. Acceptable risk

   a. People in U.S. = 2.2×10^8
   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



a. Various mathematical models used for low-dose risk assessment

(1) Probit

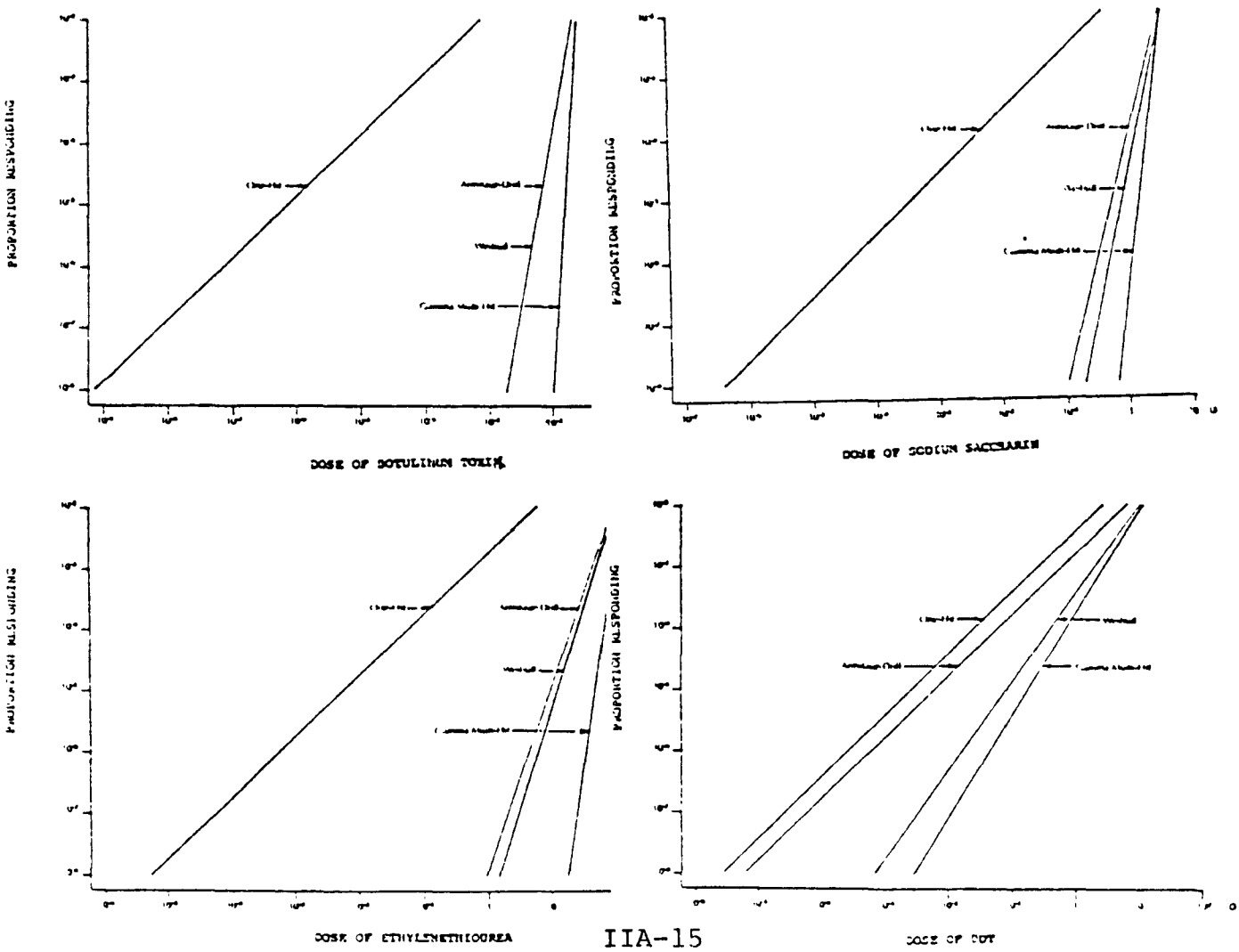
(2) Mantel-Bryan: Uses probit model with a preassigned slope of unity, this being a conservative slope. An additional conservative feature is the use of the upper 99% confidence limit of the response rather than the observed response for extrapolation.

(3) One-hit: Essentially a straight line from the bottom data point to the origin

(4) Armitage-Doll: Much more liberal than one-hit

(5) Weibull: Slightly more liberal than one-hit

(6) Gamma Multi-Hit: Slightly more liberal than Weibull



Part IIB

Principles of Absorption, Distribution, Excretion & Metabolism of Chemicals

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.

B. Special Transport

1. Active transport: characteristics of
   a. Moved against an electrochemical gradient
   b. can be saturated
   c. Selective - certain basic chemical structure -competition
   d. Requires energy
2. Facilitated diffusion: characteristics of active transport but does not move against a concentration gradient
3. Phagocytosis and pinocytosis

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 venon
   b. Nitrate to nitrite in newborns
   c. Nitrite plus amines to nitrosamines
   d. Intestinal flora degrade DDT to DDE
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. Aerosol deposition
      a. Nasopharyngeal - 5 um or larger
      b. Tracheobronchiolar - 1 to 5 um
      c. Alveolar - 1 um
   2. Mucociliary transport
   3. 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
        a. Liquids
    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: conjugation or synthesis

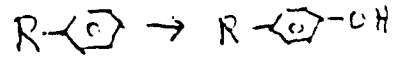
D. Location: mainly liver, but all tissues can

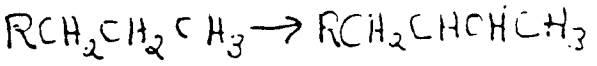
E. Qualitative

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 

3) N, O and S-dealkylation $R\text{-}(\overset{H}{N},O,S)\text{-}CH_3 \rightarrow R(NH_2, OH, SH)$

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

5) Desulfuration $R_1R_2\overset{S}{\overset{\|}{P}}\text{-}X \rightarrow R_1R_2\overset{O}{\overset{\|}{P}}\text{-}X + S$

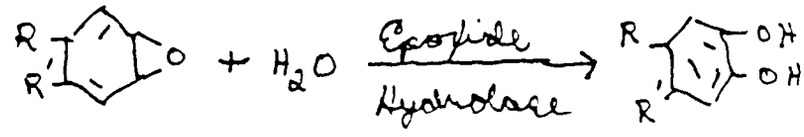
6) Sulfoxidation $RSR_1 \rightarrow R\text{-}\overset{O}{\overset{\|}{S}}\text{-}R$

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

c. Non P-450

1) Amine oxidase - not P-450

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



3) Esterases and amidases

$CH_3\overset{O}{\overset{\|}{C}}\text{-}OC_2H_5 \rightarrow CH_3\overset{O}{\overset{\|}{C}}OH + CH_3CH_2OH$

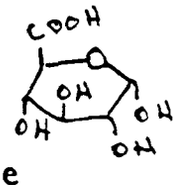
ethyl acetate — acetic acid — ethanol

4) Alcohol and aldehyde dehydrogenase

$CH_3CH_2OH + NAD^+ \rightarrow CH_3\overset{O}{\overset{\|}{C}}H \rightarrow CH_3\overset{O}{\overset{\|}{C}}\text{-}OH$

acetaldehyde — 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

Part IIC

Toxicology of Inorganics

HEAVY METALS

CURTIS D. KLAASSEN, PH.D.

I. LEAD

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

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 concentrtion
    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 inorganic

II. MERCURY

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 neuropsychiatric: 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

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

B. Toxicity Rating:

$RAs\text{-}X < As^{+5} < As^{+3} < AsH_3$

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

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. Itai-itai (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 ug 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

V. 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. 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

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. Essential element
2. Wilson's disease
3. Therapy -- penicallamine

H. Fluoride

1. Reduce dental caries at 0.7 - 1.2 mg/l or ppm
2. Dental fluorosis (discoloration and/or pitting) in childred above 2 ppm
3. Brittle bones at higher concentrations
4. MCL = 4 ppm
   SMCL = 2 ppm

J. Manganese

1. Managanese 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

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 man -- 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

Part IID

Toxicology of Pesticides

Part IID

PESTICIDES

INTRODUCTION AND HISTORY:

BENEFITS OF PESTICIDES:

1. Control of vector-born disease (malaria, yellow fever, typhus, plague)
2. Food production, transport and storage
3. Urban Pest Control

RISKS OF PESTICIDES:

1. Occupational injury (formulators, applicators, pickers)
2. Non-occupational poisoning (accidental, intentional)
3. Environmental effects (birds, fish)
4. a. pre-DDT
   b. DDT era
   c. post-DDT

DEFINITIONS:

1. Pesticide: a) Any substance or mixture of substances intended for preventing, destroying, repelling or mitigating any pest (insect, rodent, nemotode, fungus, weed, other forms of terrestrial or aquatic plant or animal life, or viruses, bacteria or other microorganisms except viruses, bacteria, or other microorganisms on or in living man or other animals) which the administrator declares to be a pest.

   b) Any substance or mixture of substances intended for use as a plant regulator, defoliant or desiccant.

2. Active ingredient, technical chemical, manufacturing use product, formulated product, etc.

3. Vehicle, excipients, solvents, binders, stickers, spreaders, emulsifiers, inerts, synergists, etc.

4. Application methods: granular, wettable powder, ULV spray, IPM.

CLASSIFICATION OF PESTICIDES:

1. Insecticides
2. Herbicides
3. Fungicides
4. Rodenticides
5. Fumigants
6. Repellants
7. Nematocides
8. Molluscucides
9. Algicides
10. Miscellaneous: defoliants, growth regulators, desiccants, miticides, sterilants

INSECTICIDES:

1. Organic phosphates (OP's)
2. Cholinergic carbamates (carbaryl, aldicarb, etc.)
3. Chlorinated hydrocarbons (DDT, lindane, etc.)
4. Botanicals (pyrethrums, nicotine, strychnine)
5. Organic nitrogen derivatives (DNOC, dinitrophenol)
6. Organic sulfur derivatives (aramite)
7. Organic thiocyanates (lethane)
8. Petroleum products (fuel oil, kerosene)
9. Stomach poisons (metals, fluorine derivatives, etc.)
10. Repellants (phthalates, indalones)

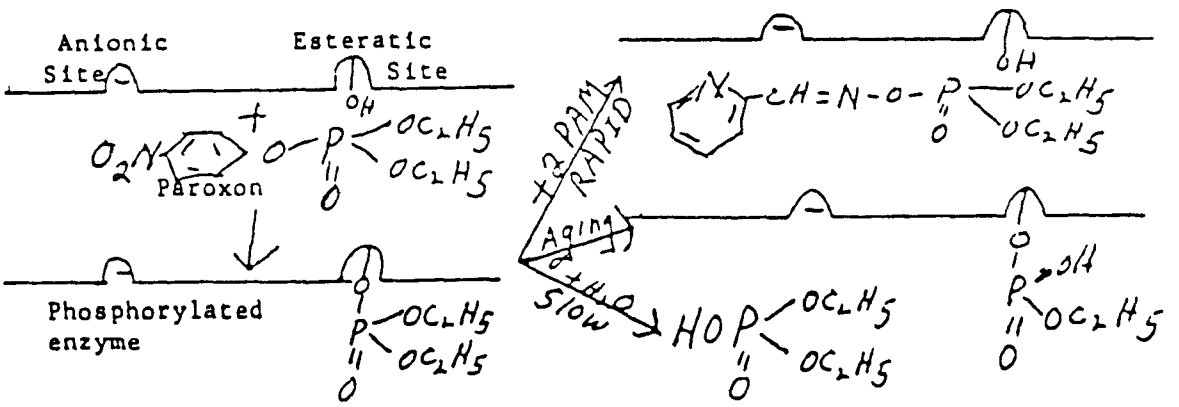
ORGANIC PHOSPHATE INSECTICIDES:

Classification: see Table 16-4

1. Direct acting
2. Indirect acting (P450 activation)

Mechanism of Action:

1. Activation to oxon
2. Detoxification by hydrolysis
3. Potentiation
4. Phosphorylation of receptor site for acetylcholine



Symptoms of Poisoning

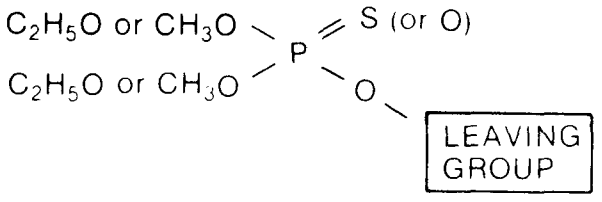
1. Cholinergic (muscarinic, nicotinic)
2. Death due to respiratory failure
3. Residual effects (neuromuscular paralysis)

Treatment of Poisoning:

1. Atropine
2. Praladoxime (2-PAM)

ORGANOPHOSPHATE CHOLINESTERASE-INHIBITING PESTICIDES

GENERAL CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS*

Highly toxic: tetraethyl pyrophosphate (TEPP), phorate (Thimet), disulfoton† (Di-Syston), fensulfothion (Dasanit), demeton† (Systox), terbufos (Counter), mevinphos (Phosdrin), methidathion (Supracide), chlormephos (Dotan, MC2188), sulfotepp (Bladafum, Dithione), chlorthiophos (Celathion), monocrotophos (Azodrin), fonofos (Dyfonate), prothoate (Fac), fenamiphos (Nemacur), phosfolan (Cyolane), methyl parathion (Dalf, Penncap-M), schradan (OMPA), chlorfenvinphos (Birlane), ethyl parathion (Parathion, thiophos), azinphos-methyl (Guthion), phosphamidon (Dimecron), methamidophos (Monitor), dicrotophos (Bidrin), isofenphos (Amaze, Oftanol), bomyl (Swat), carbophenothion (Trithion), EPN, famphur, (Warbex, Bo-Ana, Famfos), fenophosphon (Agritox, trichloronate), dialifor (Torak), cyanofenphos (Surecide).

Moderately toxic: bromophos-ethyl (Nexagan), leptophos (Phosvel), dichlorvos (DDVP, Vapona), coumaphos (Co-Ral), ethoprop (Mocap), quinalphos (Bayrusil), triazophos (Hostathion), demeton-methyl† (Metasystox), propetamphos (Safrotin), chlorpyrifos (Lorsban, Dursban), sulprofos (Bolstar), dioxathion (Delnav), isoxathion (Karphos), phosalone (Zolone), thiometon (Ekatin), heptenophos (Hostaquick), crotoxyphos (Ciodrin), cythioate (Proban), phencapton (G28029), DEF (De-Green, E-Z-off D), ethion, dimethoate (Cygon, De-Fend), fenthion (Baytex, Entex, Tiguvon, Spotton, Lysoff), dichlofenthion (Mobilawn), EPBP (S-Seven), diazinon (Spectracide), phosmet (Imidan, Prolate), formothion (Anthio), profenofos (Curacron), naled (Dibrom), phenthoate, trichlorfon (Dylox, Dipterex, Neguvon), pyrazophos (Afugan, Curamil), fenitrothion (Agrothion, Sumithion), cyanophos (Cyanox), pyridaphenthion (Ofunack), propylthiopyrophosphate (Aspon), acephate (Orthene), merphos (Folex), malathion (Cythion), etrimfos (Ekamet), phoxim (Baythion), pirimiphosmethyl (Actellic), iodofenphos (Nuvanol-N), bromophos (Nexion), tetrachlorvinphos (Gardona, Rabon), temephos (Abate, Abathion).

* These are listed approximately in order of descending toxicity. "Highly toxic" organophosphates have listed oral LD_{50} values (rat) less than 50 mg/kg; "moderately toxic" agents have LD_{50} values in excess of 50 mg/kg.

† These organophosphates are systemic; i.e., they are taken up by the plant and translocated into foliage and sometimes into the fruit.

TOXICOLOGY

Organophosphates poison insects and mammals primarily by phosphorylation of the acetylcholinesterase enzyme at nerve endings. The enzyme is critical to normal transmission of nerve impulses from nerve fibers to innervated tissues. Some critical proportion of the tissue enzyme mass must be inactivated by phosphorylation before symptoms and signs of poisoning are manifest. At sufficient dosage, loss of enzyme function allows accumulation of acetylcholine (the impulse-transmitter substance) at cholinergic neuroeffector junctions (muscarinic effects), and at skeletal myoneural junctions and in autonomic ganglia (nicotinic effects). Organophosphates also impair nerve impulse transmission in the brain, causing disturbances in sensorium, motor function, behavior, and respiratory drive. Depression of respiration is the usual cause of death in organophosphate poisoning. Recovery depends ultimately on generation of new enzyme.

Organophosphates are efficiently absorbed by inhalation, ingestion, and skin penetration. To a degree, toxicity depends on the rate at which specific organophosphates are metabolized in the body (principally by hydrolysis in the liver), thus limiting the amount of pesticide available to attack acetylcholinesterase enzyme in other tissues.

Many organophosphates readily undergo conversion from -thions to -oxons (replacement of sulfur by oxygen). In general, -oxons are much more toxic than -thions. This conversion occurs in the environment under the influence of sunlight and in the body, mainly by the action of liver microsomes. Ultimately, both -oxons and -thions are inactivated by hydrolysis at the ester linkage, yielding alkyl phosphates and phenols which are readily excreted. The hydrolysis products present little toxic hazard.

One to two days after organophosphate absorption, depending on the specific organophosphate, some phosphorylated acetylcholinesterase enzyme can be de-phosphorylated (reactivated) by certain oxime antidotes. After this interval, the nature of the enzyme-phosphoryl bond changes, rendering the enzyme inactivation irreversible. New enzyme must then be generated.

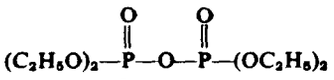
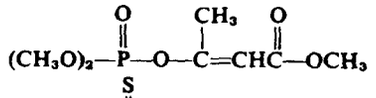
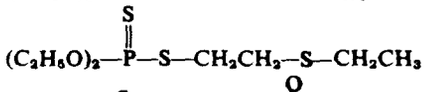
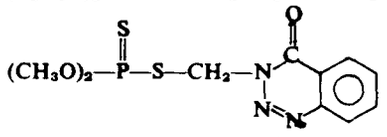
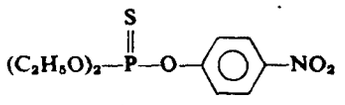
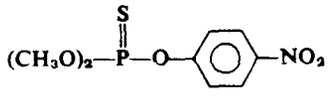
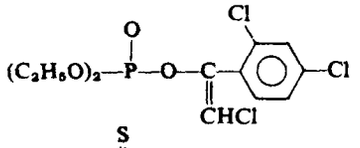
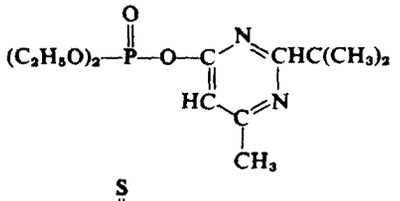
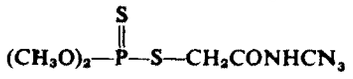
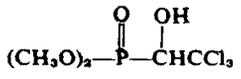
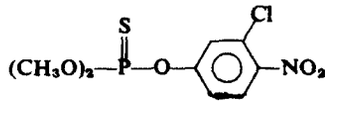
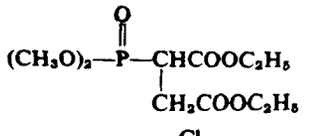
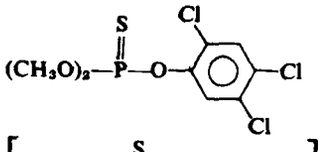
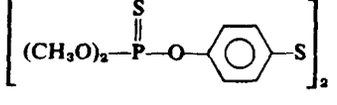
Very rarely, organophosphate pesticides have produced a different type of neurotoxicity, consisting of damage to the myelin substance of peripheral nerves. This leads to a protracted peripheral neuropathy, characterized by numbness, pain, and weakness in the extremities, which persists for months or years. Organophosphates associated with these chronic illnesses have included some whose acute toxic potential is low; i.e., there appears to be no relationship between acute toxicity and the likelihood of a chronic neuropathic effect. Particularly suspect as neurotoxic agents of this type are the phenylphosphonothioate series, cyanofenphos, EPN, leptophos, and EPBP.

Other unusual properties of specific organophosphates may render them more hazardous than basic toxicity data suggest. By-products can develop in long-stored malathion which strongly inhibit the hepatic enzymes operative in malathion catabolism, thus enhancing its toxicity. Certain organophosphates are exceptionally prone to storage in fat tissue, prolonging the need for antidote when stored pesticide is released back into the circulation. It is possible that other unrecognized factors modify the toxicity of organophosphates.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

Symptoms of acute poisoning develop during exposure or within 12 hours (usually within four hours) of contact. **HEADACHE, DIZZINESS, WEAKNESS, INCOORDINATION, MUSCLE TWITCHING, TREMOR, NAUSEA, ABDOMINAL CRAMPS, DIARRHEA,** and **SWEATING** are common early symptoms. Blurred or dark vision, confusion, tightness in the chest, wheezing, productive cough, and **PULMONARY EDEMA** may occur. Incontinence, unconsciousness and convulsions indicate very severe poisoning. **SLOW HEARTBEAT,** salivation, and tearing are common. **TOXIC PSYCHOSIS,** with manic or bizarre behavior, has led to misdiagnosis of acute alcoholism. Slowing of the heartbeat may rarely progress to complete sinus arrest. **RESPIRATORY DEPRESSION** may be fatal. Continuing daily absorption of organophosphate at intermediate dosage may cause an **INFLUENZA-LIKE ILLNESS** characterized by weakness, anorexia, and malaise.

The very few individuals who have suffered peripheral neuropathy following organophosphate exposure exhibited diverse clinical courses. Onset of symptoms was generally slow, sometimes after an asymptomatic interval of several days following exposure. Principal symptoms have been numbness, tingling, pain and weakness of the arms and legs. Some recovered fully in a few weeks; a few others experienced muscle atrophy, leaving a degree of paresis and sensory loss.

COMPOUND	STRUCTURE	LD50 IN MALE RATS (mg/kg)*		"NO EFFECT LEVEL"†	ADI‡
		Oral	*Dermal*	*(mg/kg/day)*	*(mg/kg)*
TEPP		1.1	2.4	—	—
Mevinphos		6.1	4.7	—	—
Disulfoton		6.8	15	—	—
Azinphosmethyl		13	220	Rat—0.125 Dog—0.125	0.0025
Parathion		13	21	Rat—0.05 Man—0.05	0.005
Methylparathion		14	67	—	—
Chlorfenvinphos		15	31	Rat—0.05 Dog—0.05	0.002
Dichlorvos		80	107	Rat—0.5 Dog—0.37 Man—0.033	0.004
Diazinon		108	200	Rat—0.1 Monkey—0.05 Dog—0.02 Man—0.02	0.002
Dimethoate		215	260	Rat—0.4 Man—0.04	0.02
Trichlorfon		630	>2,000	Rat—2.5 Dog—1.25	0.01
Chlorothion		880	1,500–4,500		
Malathion		1,375	>4,444	Rat—0.5 Man—0.2	0.02
Ronnel		1,250	>5,000	Rat—0.5 Dog—1.0	0.01
Abate		8,000	>4,000		

* Values obtained in standardized tests in the same laboratory (Gaines, 1969). *(continued)*

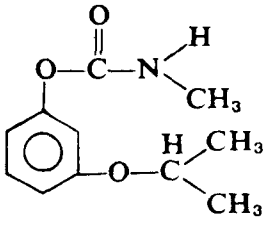
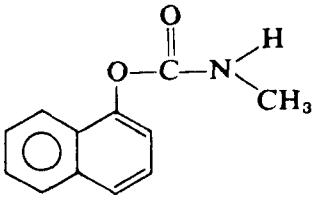
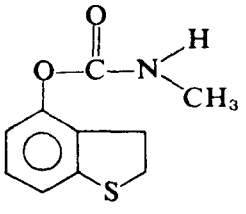
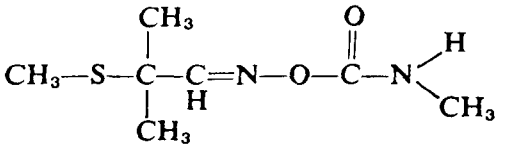
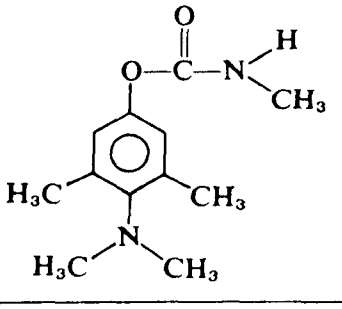
† Maximum rate of intake (usually for three-month to two-year feeding studies) that was tested and did *not* produce significant toxicologic effects (as listed in the monographs issued jointly by the Food and Agriculture Organization of the United Nations and the World Health Organization, as developed by joint meetings of expert panels on pesticide residues held annually, 1965–1972).

‡ Acceptable daily intake (ADI) = the daily intake of a chemical that, during a lifetime, appears to provide the practical certainty that injury will not result (in man) during a lifetime of exposure. Figures taken from World Health Organization (1973).

CHOLINERGIC CARBAMATE INSECTICIDES:

Chemistry: see Table 16-6

Table 16-6. EXAMPLES OF RANGE OF ACUTE TOXICITIES OF SOME CARBAMATE INSECTICIDES

		LD50 IN MALE RATS* (mg/kg)	
		Oral	*Dermal*
Baygon (Propoxur)		83	> 2,400
Carbaryl		850	> 4,000
Mobam		150	> 2,000
Temik (Aldicarb)		0.8	3.0
Zectran		37	1,500–2,500

* Values obtained in standardized tests in the same laboratory (Gaines, 1969).

Symptoms of Poisoning:

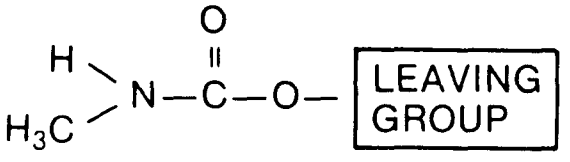
1. Carbamylation of receptor site for acetylcholine
2. Cholinergic effects (muscarinic)

Treatment of Poisoning:

1. Atropine

CARBAMATE CHOLINESTERASE-INHIBITING PESTICIDES

GENERAL CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS*

Highly toxic:** aldicarb† (Temik), oxamyl (Vydate), carbofuran (Furadan), methomyl (Lannate, Nudrin), formetanate HCl (Carzol, Dicarzol), aminocarb (Matacil), dimetilan (Snip Fly Bands).

Moderately toxic*:** promecarb (Carbamult), methiocarb (Mesurol, Draza), propoxur (Baygon), pirimicarb (Pirimor, Aphox, Rapid), bufencarb (Bux), carbaryl (Sevin).

TOXICOLOGY

Insecticides of this class cause reversible carbamylation of acetylcholinesterase enzyme, allowing accumulation of acetylcholine at cholinergic neuroeffector junctions (muscarinic effects), and at skeletal muscle myoneural junctions and in autonomic ganglia (nicotinic effects). Poison also impairs CNS function. The carbamyl-enzyme combination dissociates more readily than the phosphorylated enzyme produced by organophosphate insecticides. This lability tends to mitigate the toxicity of carbamates, but also limits the usefulness of blood enzyme measurements in diagnosis of poisoning. Carbamates are absorbed by inhalation, ingestion, and dermal penetration. They are actively metabolized by the liver, and the degradation products are excreted by the liver and kidneys.

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* Listed approximately in order of decreasing toxicity.

** Acute oral LD_{50} in the rat less than 50 mg/kg.

*** Acute oral LD_{50} in the rat above 50 mg/kg.

† This carbamate is a systemic, i.e., it is taken up by the plant and translocated into foliage and sometimes into the fruit.

CHLORINATED HYDROCARBON INSECTICIDES:

Classification:

1. Chlorinated ethanes (DDT, Methoxychlor)
2. Cyclodienes (aldrin, dieldrin, endrin, chlordane, heptachlor, endosulfan
3. Others: lindane, toxaphene, mirex, kepone

Chemistry: see Figure 16-7

1. Solubility
2. Biomagnification

Mechanism of Action:

Symptoms of Poisoning:

1. CNS effects (epileptiform convulsions)
2. Liver effects
3. Effects on fish and birds

Treatment of Poisoning:

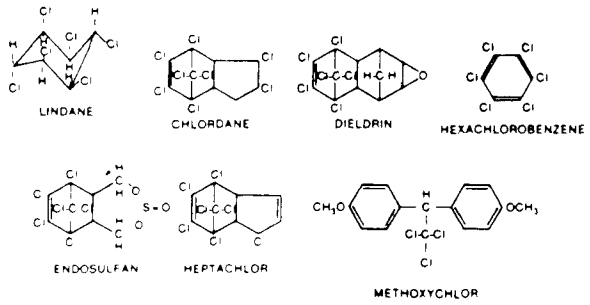
1. Anticonvulsants
2. Cholistyramine

Toxicology:

1. DDT and methoxychlor
2. Cyclodienes
3. Lindane and BHC
4. Mirex and kepone

SOLID ORGANOCHLORINE PESTICIDES

CHEMICAL STRUCTURES



COMMON COMMERCIAL PESTICIDE PRODUCTS*

Highly toxic: endrin (Hexadrin), a stereoisomer of dieldrin.

Moderately toxic: aldrin (Aldrite, Drinox), endosulfan (Thiodan), dieldrin (Dieldrite), toxaphene (Toxakil, Strobane-T), lindane (Gammexane), benzene hexachloride (BHC, HCH), DDT (chlorophenothane), heptachlor, kepone, terpene polychlorinates (Strobane), chlordane (Chlordan), dicofol (Kelthane), chlorobenzilate (Acaraben), mirex, methoxychlor (Marlate), dienochlor (Pentac), hexachlorobenzene (HCB), ethylan (Perthane). All except HCB are insecticides or acaricides; HCB is a fungicide.

TOXICOLOGY

Most organochlorines are efficiently absorbed from the gut and across the skin. In adequate dosage, they interfere with axonic transmission of nerve impulses and, therefore, disrupt the function of the nervous system, principally that of the brain. This results in behavioral changes, sensory and equilibrium disturbances, involuntary muscle activity, and depression of vital centers, particularly those controlling respiration. Adequate doses of some organochlorines increase myocardial irritability, and stimulate synthesis of hepatic drug-metabolizing enzymes.

Chlordane has apparently induced a few cases of self-limited megaloblastic anemia after protracted low-level exposures. The condition has resolved following termination of exposure.

Kepone has caused nervousness, tremor, incoordination, weakness and infertility in excessively exposed workers. Clinical improvement has occurred as the pesticide was excreted.

Endrin is more toxic to the liver and kidneys than the other organochlorines at comparable dosages.

Prolonged ingestion of HCB-treated grain produced porphyria cutanea tarda in several thousand Turkish citizens who mistakenly ate the seed grain. Disease was manifest as excretion of red urine, bullous dermatitis, hyperpigmentation, generalized hair growth, muscle wasting and liver enlargement. Slow improvement occurred when HCB ingestion was stopped.

A series of anecdotal reports of bone marrow injury has tended to indict lindane as a hematotoxic agent in certain predisposed individuals, but no relationship has been proved.

Lindane, methoxychlor, terpene polychlorinates, chlorobenzilate, dicofol, and the constituents of chlordane, except heptachlor and oxychlordane, are excreted rapidly by humans, usually within 3-4 days of ingestion. Dieldrin, aldrin, endrin, hexachlorobenzene, heptachlor, and oxychlordane are excreted within weeks to several months of absorption by humans. DDT, kepone, mirex, and the beta isomer of benzene hexachloride are excreted very slowly, requiring months or years for elimination. The excretion kinetics of perthane, kelthane, and dienochlor are not known. Because of their lipophilicity, all organochlorines are likely to be excreted in the milk of lactating women.

* Listed approximately in order of decreasing toxicity.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

APPREHENSION, EXCITABILITY, DIZZINESS, HEADACHE, DISORIENTATION, WEAKNESS, PARESTHESIAE, muscle twitching, tremor, tonic and clonic **CONVULSIONS** (often epileptiform), and unconsciousness are the major manifestations. Soon after ingestion, nausea and vomiting commonly occur. When chemicals are absorbed dermally, apprehension, twitching, tremors, confusion, and convulsions may be the first symptoms. Respiratory depression is caused by the pesticide and by the petroleum solvents in which these pesticides are usually dissolved. Pallor occurs in moderate to severe poisoning. Cyanosis may result as convulsive activity interferes with respiration.

Even though convulsive activity may be severe, the prognosis in poisonings by these agents is far from hopeless. Although fatalities have occurred following absorption of large amounts of some organochlorines, there is a substantial likelihood of complete recovery if convulsions can be controlled, and vital functions sustained.

Table 16-7. TOXICOLOGY OF SOME ORGANOCHLORINE INSECTICIDES

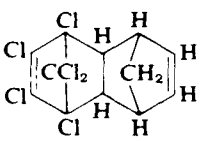
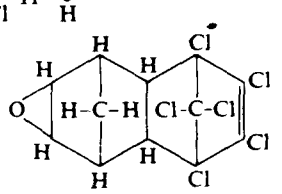
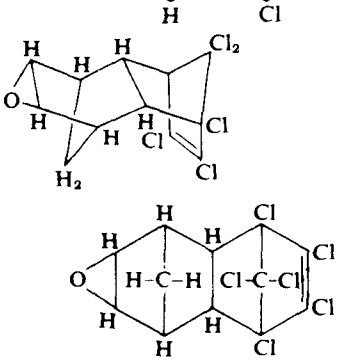
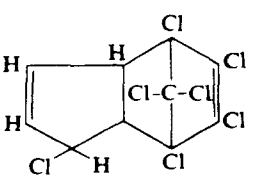
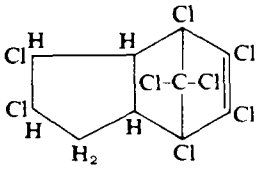
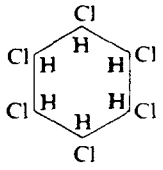
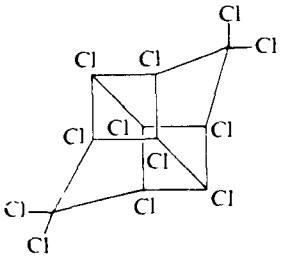
COMPOUND	STRUCTURE	LD50 IN MALE RATS ORAL	DERMAL (mg/kg)*	"NO EFFECT LEVEL"† (mg/kg/day)	ADI‡ (mg/kg/day)
DDT	See Figure 16-5	113 (*p,p'*-DDT) 217 (technical)	— 2510	Rat—0.05	0.005¶
DDE§	See Figure 16-5	880	—	—	—
DDA§	See Figure 16-5	740	—	—	—
Methoxychlor	See Figure 16-5	5,000-7,000	—	Rat—10	0.1
Aldrin		39	98	Rat—0.025 Dog—0.025	0.0001
Dieldrin		46	90	Rat—0.025 Dog—0.025	0.0001
Endrin		18	18	Rat—0.05 Dog—0.025	0.0002
Heptachlor		100	195	Rat—0.25 Dog—0.06	0.0005

Table 16-7. (*continued*)

COMPOUND	STRUCTURE	LD50 IN MALE RATS ORAL	DERMAL (mg/kg)*	"NO EFFECT LEVEL"† (mg/kg/day)	ADI‡ (mg/kg/day)
Chlordane		335	840	Rat—1.0 Dog—0.06	0.001
Lindane		88	1,000	Rat—1.25	0 0125
Mirex		740	> 2,000	–	—

* Values obtained in standardized tests in the same laboratory (Gaines, 1969).
† Maximum rate of intake (usually for three-month to two-year feeding studies) that was tested and did *not* produce significant toxicologic effects (as listed in the monographs issued jointly by the Food and Agriculture Organization of the United Nations and the World Health Organization, as developed by joint meetings of expert panels on pesticide residues held annually, 1965–1972).
‡ Acceptable daily intake (ADI) = the daily intake of a chemical that, during a lifetime, appears to provide the practical certainty that injury will not result (in man) during a lifetime of exposure. Figures taken from World Health Organization (1973).
§ Metabolites of DDT.
¶ Conditional ADI pending further evaluation.

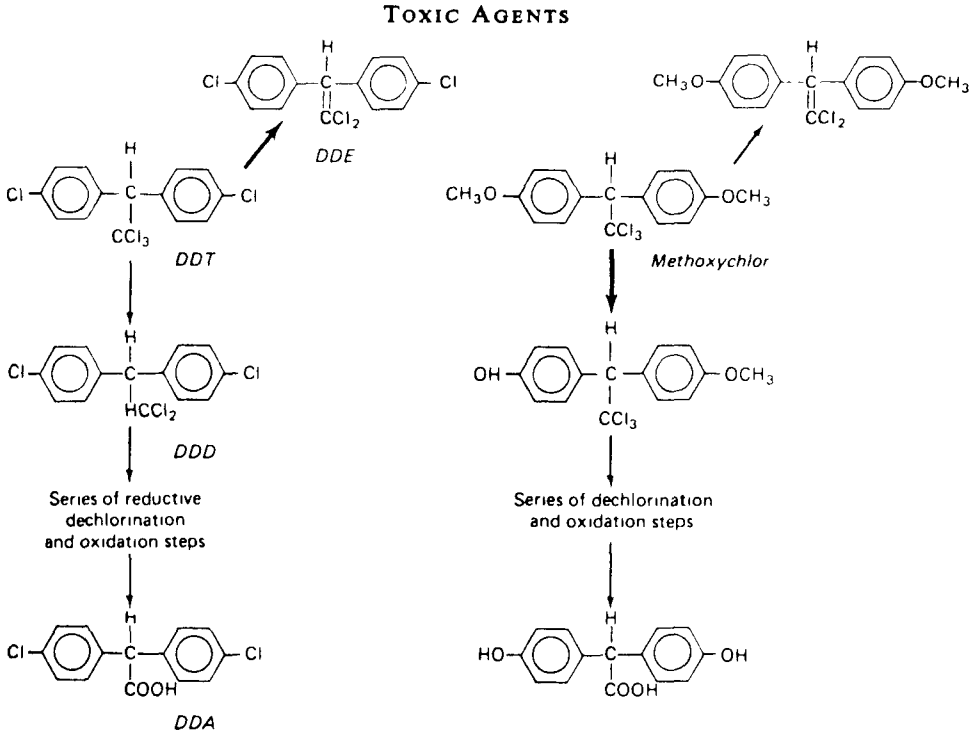


Figure 16-5. Summary comparison of major metabolic pathways for DDT and methoxychlor.

BOTANICAL INSECTICIDES:

1. Nicotine

2. Pyrethrums

3. Rotenoids

4. Strychnine

5. Resins

HERBICIDES:

Classification:

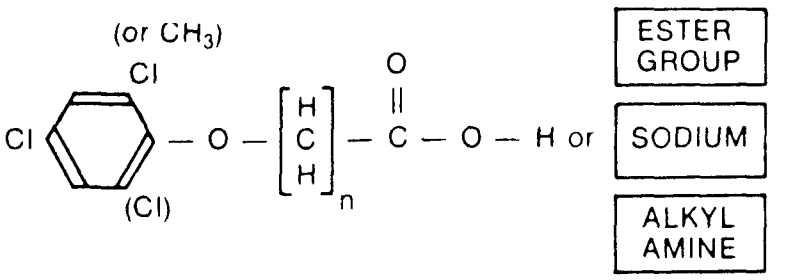
1. Phenoxy (2,4-D, 2,4,5-T, silvex, MCPA)
2. Dipyridyls (paraquat, diquat, morfamquat)
3. Dinitrophenols and analines (DNOC, trifluralin)
4. Acetanillides and acetamides (propachlor, propanil)
5. Triazines and picolinic acids (aminotriazole, picloram, atrazine)
6. Urea and uracile derivatives (diuron, bromocil)
7. Benzoic acid and phthalates (amiben, endothal)
8. Carbamates (chloropropham, propham)
9. Inorganics (chlorates, borates)
10. Miscellaneous (fuel oils, arsenates)

FUMIGANTS:

1. Methyl bromide
2. Cyanide
3. Sulfur dioxide
4. Naphthalene
5. p-Dichlorobenzene
6. Carbon tetrachloride
7. Chloropicrin
8. Ethylene dibromide
9. Dibromochloropropane
10. Miscellaneous (phosphine)

CHLOROPHENOXY COMPOUNDS

GENERAL CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS

Several hundred commercial products contain chlorophenoxy herbicides in various concentrations and combinations. Following are names of widely advertised formulations. In some cases, the same name is used for products with different ingredients. Exact composition must therefore be determined from product label.

2,4-D, or 2,4-dichlorophenoxyacetic acid (Weedone†, Agrotec, Amoxone, Aqua-Kleen, BH 2,4-D, Chipco Turf Herbicide "D", Chloroxone, Crop Rider, D50, Dacamine 4D, Ded-Weed, Desormone, Dinoxol, DMA4, Dormone, Emulsamine BK, Emulsamine E-3, Envert DT or 171, Esteron 99 Concentrate, Esteron Four, Esteron Brush Killer, Estone, Fernoxone, Fernimine, Ferxone, Fernesta, Formula 40, Hedonal, Herbidal, Lawn-Keep, Macondray, Miracle, Netagrone 600, Pennamine D, Planotox, Plantgard, Rhodia, Salvo‡, Spritz-Hormin/2,4-D, Spritz-Hormit/2,4-D, Superormone Concentre, Super D Weedone, Transamine, U46, Verton 2D, Visko-Rhap, Weed-B-Gon, Weedar, Weed-Rhap, Weed Tox, Weedtrol, De broussaillant 600, Lithate, Dicotox, Field Clean Weed Killer). 2,4-DB is the butyric acid homologue of 2,4-D. Dichlorprop is the propionic acid homologue.

2,4,5-T or 2,4,5-trichlorophenoxyacetic acid (Brush-Rhap, Dacamine 4T, Debroussaillant Concentre, Ded-Weed Brush Killer, Esteron 245, Fence Rider, Forron, Inverton 245, Line Rider, Spontox, Super D Weedone, Tormona, Transamine, Trinoxol, Trioxone, U46, Veon 245, Verton 2T, Weedar, Weedone Envert T).

Common mixtures of 2,4-D and 2,4,5-T are: Dacamine 2D/2T, Esteron Brush Killer, Rhodia Low Volatile Brush Killer No. 2, U46 Special, Tributon, Visko-Rhap LV2D-2T, and Transamine.

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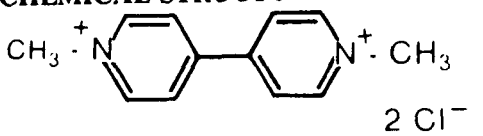
† A product of identical name containing pentachlorophenol (Chapter 4) as the active ingredient has been discontinued by Amchem Products Co.

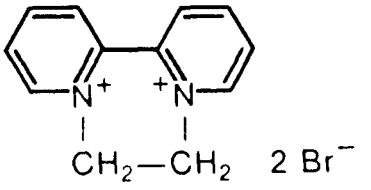
‡ A product of identical name marketed by the Crystal Chemical Company contains cacodylic acid as the active ingredient (Chapter 10).

PARAQUAT AND DIQUAT

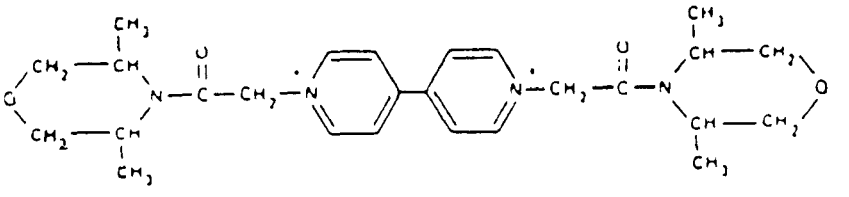
CHEMICAL STRUCTURES



PARAQUAT



DIQUAT



MORFAMQUAT

COMMON COMMERCIAL PESTICIDE PRODUCTS

Paraquat products: paraquat dichloride (usually as a 21% concentrate). Other names: Ortho paraquat-CL, Crisquat, Dextrone X, Esgram. Mixtures: Priglone, Preeglone, Weedol—with diquat; Simpar, Terraklene—with simazine; Gramonol, Mofisal—with monolinuron; Pathclear—with diquat and simazine; TotaCol, Dexuron—with diuron.

Diquat products: diquat (Reglone, Reglox, Aquacide, Dextrone, Weedtrine-D). Mixtures: Priglone, Preeglone, Weedol—with paraquat; Pathclear—with paraquat and simazine.

TOXICOLOGY

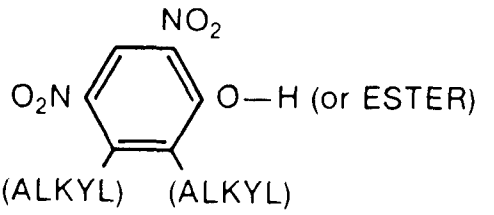
These dipyridyls injure the epithelial tissues: skin, nails, cornea, liver, kidney, and the linings of the GI and respiratory tracts. In addition to direct irritant effects, injury may involve peroxidation of intracellular and extracellular phospholipids and inhibition of surfactant synthesis by lung tissue. These toxic properties may derive from the capacity of dipyridyls to generate free radicals in tissues. The injury is usually reversible; however, the pulmonary reaction which follows ingestion of paraquat is often fatal.

Certain injuries have followed occupational contact with paraquat. Contact with the concentrate may cause irritation and fissuring of the skin of the hands, and cracking, discoloration, and sometimes loss of the fingernails. Splashed in the eye, paraquat concentrate causes conjunctivitis and, if not promptly removed, may result in protracted opacification of the cornea.

Although nearly all systemic intoxications by paraquat have followed ingestion of the chemical, occasional poisonings have resulted from excessive dermal contact. Absorption of toxic amounts is much more likely to occur if the skin is abraded. Persons who have experienced extraordinary dermal contact with paraquat (especially the concentrate) should be examined, and tested for hazardous concentrations of the agent in the blood and urine (see section on Confirmation of Diagnosis).

NITROPHENOLIC AND NITROCRESOLIC HERBICIDES

GENERAL CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS

Dinitrophenol (Chemox PE), dinitrocresol (DNOC, DNC, Sinox, Chemsect DNOC, Elgetol 30, Nitrador, Selinon, Trifocide), dinoseb (DNBP, Dinitro, Basanite, Caldon, Chemox General, Chemox PE, Chemsect DNBP, Dinitro-3, Dinitro General, Dow General Weed Killer, Dow Selective Weed Killer, Dynamyte, Elgetol 318, Gebutox, Kiloseb, Nitropone C, Premerge 3, Sinox General, Subitex, Unicrop DNBP, Vertac Dinitro Weed Killer), dinosam (DNAP), dinoprop, dinoterbon, dinoterb, dinosulfon, binapacryl (Morocide, Endosan, Ambox, Dapacryl), dinobuton (Acrex, Dessin, Dinofen, Drawinol, Talan), dinopenton, dinocap (Crotothane, Karathane). Several combinations are widely used: Dyanap and Klean Krop = dinoseb + naptalam; Ancrack = sodium salts of dinoseb + naptalam; Naptro = dinitrophenol + naptalam.

TOXICOLOGY

These materials should be regarded as highly toxic to humans and animals. Most nitrophenols and nitrocresols are well absorbed from the gastrointestinal tract, across the skin, and by the lung when fine droplets are inhaled. Except in a few sensitive individuals, aromatic nitro-compounds are only moderately irritating to the skin. Like other phenols, they are toxic to the liver, kidney, and nervous system. The basic mechanism of toxicity is a stimulation of oxidative metabolism in cell mitochondria, by interference with the normal coupling of carbohydrate oxidation to phosphorylation (ADP to ATP). Increased oxidative metabolism leads to pyrexia, tachycardia, and dehydration, and ultimately depletes carbohydrate and fat stores. Most severe poisonings from absorption of these compounds have occurred in workers who were concurrently exposed to hot environments. Pyrexia and direct action on the brain cause cerebral edema, manifest clinically as a toxic psychosis and sometimes convulsions. Liver parenchyma and renal tubules show degenerative changes. Albuminuria, pyuria, hematuria, and increased BUN are often prominent signs of renal injury.

Agranulocytosis has occurred in humans following large doses of dinitrophenol. Cataracts have occurred in some chronically poisoned laboratory species, but this effect has not been observed in humans.

Nitrophenols and nitrocresols are efficiently excreted by the kidneys, and there is some hepatic excretion into the bile. Unless the absorbed dose was extremely high, or kidney function is impaired, nearly complete elimination from the body can be expected within 3-4 days.

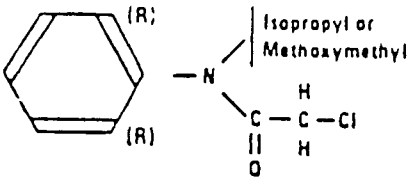
Death in nitrophenol poisoning is followed promptly by intense rigor mortis.

ORGANONITROGEN HERBICIDES

CLASSES OF ORGANONITROGEN HERBICIDES AND COMMON COMMERCIAL PRODUCTS

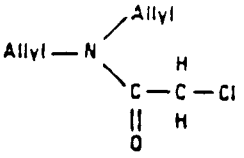
X = HALOGEN R = ALKYL

ACETANILIDE DERIVITIVES



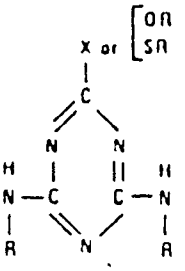
propachlor (Ramrod),
alachlor (Lasso)
propanil (DPA, Propanex, Stam F-34)

ACETAMIDE COMPOUNDS



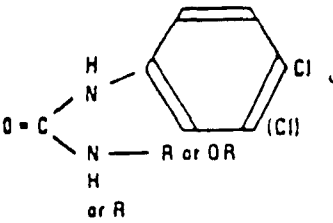
allidochlor (Randox, CDAA)

s-TRIAZINE COMPOUNDS



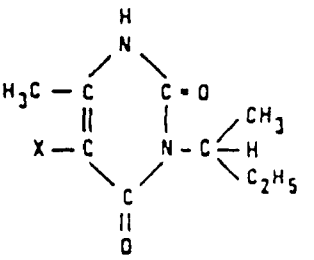
atrazine (Aatrex, Atranex, Gesaprim, Primatol A)
simazine (Princep, Primatol S, Simazex, Gesatop)
propazine (Milogard, Gesamil, Primatol P)
prometone (Pramitol, Gesafram, prometon)
atraton (Atratone)
prometryn (Caparol, Gesagard, Primatol Q, Prometrex)
ametryn (Evik, Ametrex, Gesapax)
desmetryn (Semeron)
terbutryn (Igran, Shortstop F)
cyanazine (Bladex, Seppic)
cyprazine (Outlook)

UREA DERIVITIVES



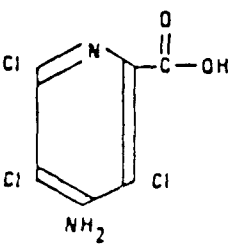
monuron (Monurex, Telvar)
diuron (Di-on, durex, Karmex, Vondiuron)
linuron (HOE-2810, Afalon, Lorox, Sarclex)

URACIL DERIVITIVES



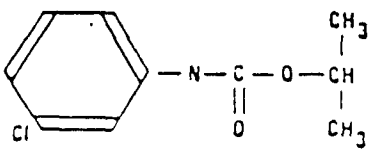
bromacil (Borea, Hyvar X, Hyvar X-L, Borocil IV, Urox HX or H, Isocil)
terbacil (Sinbar)

PICOLINIC ACID DERIVITIVES



picloram (Tordon, Borolin)

CARBAMATE COMPOUNDS

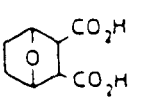


chlorpropham (Chloro IPC, CIPC, Furloe)

Benzoic acid & Phthalate Derivatives

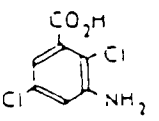
Endothall

7-Oxabicyclo (2,2,1) heptane-2,3 dicarboxylic acid



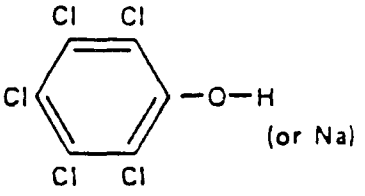
Chloramben

3-Amino-2,5-dichlorobenzoic acid



PENTACHLOROPHENOL OR SODIUM PENTACHLOROPHENATE

CHEMICAL STRUCTURE



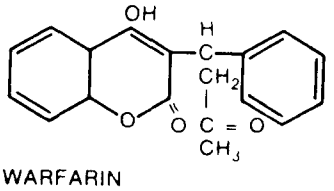
COMMON COMMERCIAL PESTICIDE PRODUCTS

PCP, Dowicide-7, Penchlorol, Pentacon, Penwar, Weedone, Veg-I-Kill, Wood Preserver, Wood Tox 140, Purina Insect Oil Concentrate, Gordon Termi Tox, Usol Cabin Oil, Certified Kiltrol-74 Weed Killer, Ciba-Geigy Ontrack OS 3, 4 or 5, Ortho Triox Liquid Vegetation Killer, Black Leaf Grass Weed and Vegetation Killer Spray.

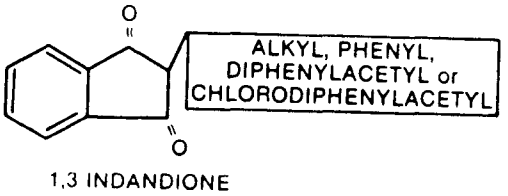
Pentachlorophenol has many uses as a weed killer, defoliant, wood preservative, germicide, fungicide, and molluscicide. It is an ingredient of many other formulated mixtures sold for one or more of these purposes.

ANTICOAGULANT RODENTICIDES

STRUCTURES OF PRINCIPAL CLASSES



WARFARIN



1,3 INDANDIONE

COMMON COMMERCIAL PESTICIDE PRODUCTS

Coumarin type: warfarin (Kypfarin, Warf-42, D-Con, Warfeide, Prolin), coumafuryl (Fumarin), Dethmor, Rax

1,3-indandione type: diphacinone, or diphenadione (Ramik), chlorophacinone (Drat, Caid, Liphadione, Microzul, Ramucide, Rotomet, Raviac, Topitox), pindone (Pivalyn, Pivacin, Tri-ban, Pival), valone, (PMP).

These materials are commonly added to baits or dissolved in small amounts of water for pest rodents to drink. One hundred grams of the prepared commercial baits must be ingested to yield 25 mgm of anticoagulant. Rodenticide "drinks" are made by adding dry concentrate (0.54 gm of active ingredient per 100 gm of powder) to specified volumes of water. The poison in the concentrate is coated on sugar or sand to facilitate measurement and handling.

RODENTICIDES:

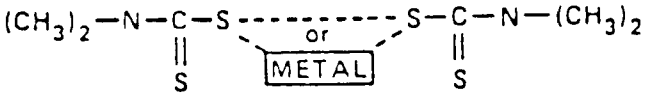
1. Warfarin
2. Red squill
3. Sodium flouroacetate (1080)
4. Phosphorus and phosphides
5. ANTU
6. Thallium
7. Vacor

FUNGICIDES:

1. Metals
   a. copper derivatives
   b. mercury derivatives
2. Halogens
   a. chlorine group
   b. iodine group
   c. bromine group
3. Dithiocarbamates
4. Phthalimides (captan, folpet)
5. Miscellaneous (borax, salicylanilide, carbolineum)

DIMETHYLDITHIOCARBAMATE COMPOUNDS*

GENERAL CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS

Tetramethyl thiuram disulfide
Thiram (Arasan, Thiramad, Thirasan, Thylate, Tiramipa, Pomasol forte, TMTDS Thiotex, Fernasan, Nomersan, Tersan, TUADS)

Metallodimethyldithiocarbamates
Ziram, Pomasol Z forte (zinc), Fermam (iron), Vapam (sodium)

Part IIE

Toxicology of Solvents and Vapors

Toxicology of Solvents and Vapors

SOLVENTS AND VAPORS

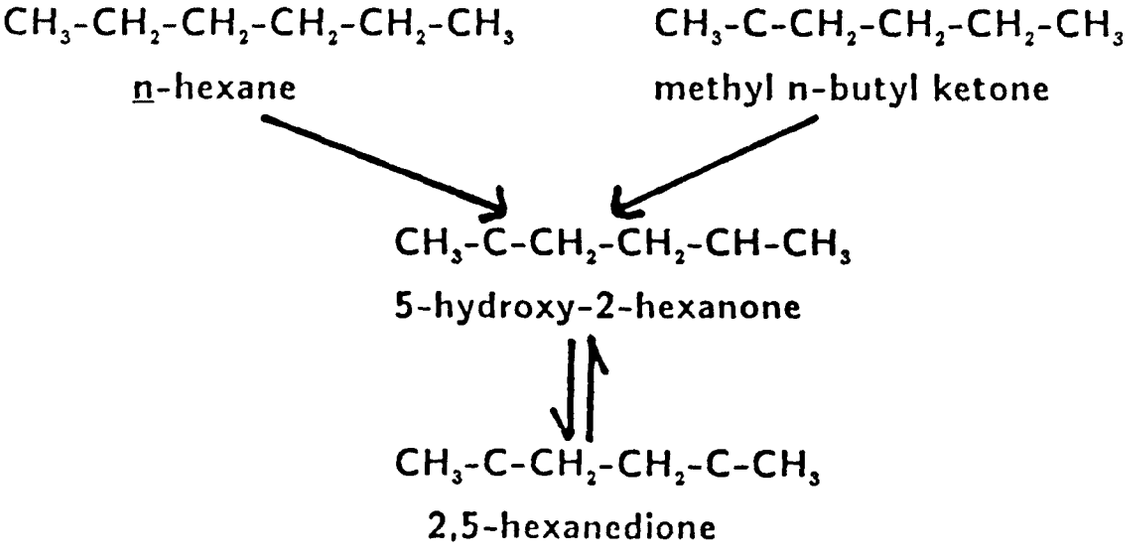
CURTIS D. KLAASSEN, PH.D.

I. C_1-C_4 ALIPHATIC HYDROCARBONS

- A. Methane -- natural gas -- asphyxia
- B. Ethane -- natural gas -- asphyxia
- C. Propane -- bottled gas -- CNS depression
- D. Butane -- bottled gas -- CNS depression

II. C_5-C_8 ALIPHATIC HYDROCARBONS

- A. Produce CNS depression
- B. n-Hexane
  1. CNS depression
  2. Polyneuropathy
     - a. Muscular weakness and sensory impairment of extremities
     - b. Demyelination and axonal degeneration
     - c. Also produced by methyl n-butyl ketone



III. GASOLINE AND KEROSENE

A. CNS depression -- death from respiratory failure

B. Sensitize myocardium to epinephrine -- ventricular fibrillation

C. Aspiration -- chemical pneumonitis

IV. HALOGENATED HYDROCARBONS

A. General characteristics

1. Excellent solvents
2. Low flammability
3. Depress CNS

B. Carbon tetrachloride

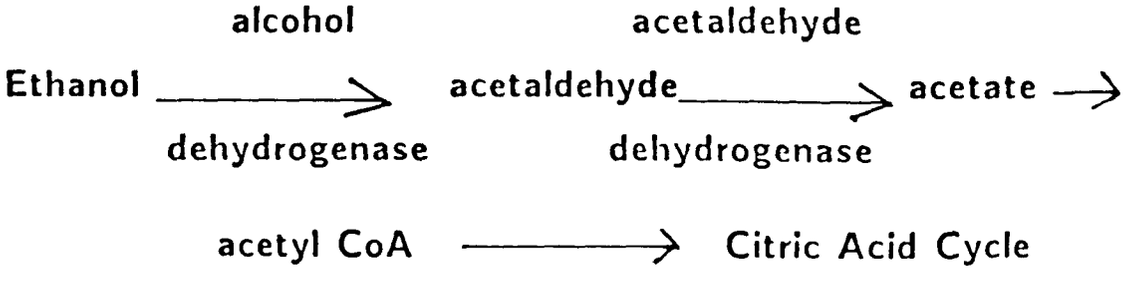
1. Use -- hookworm, anesthetic, spot remover, solvent
2. Toxic effects
   a. CNS depression
   b. Sensitize myocardium to catecholamine
   c. Kidney injury
   d. Liver injury
      1) Mechanism
         a) Biotransformed by P-450 to trichloromethyl free radical
         b) Attacks membrane lipids and produces lipid peroxidation
      2) Alcohol potentiation
         a) Ethanol
         b) Isopropanol
   e. Carcinogenic

C. Other halogenated hydrocarbons

	CNS Depression	Sensitize 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	+		++	-	+++
(vinly chloride)					
1,1-Dichloroethylene	+		+++	-	+
(vinylidine chloride)					
1,2-Trans-dichloroethylene	+		++		
Trichloroethylene	+	+	+-	-	+
Tetrachloroethylene (perchloroethylene)	+	-	+-	+-	+

V. ALIPHATIC ALCOHOLS. Ethanol effects

1. Acute effects
   a. CNS depression
   b. Diuresis -- volume and inhibition of ADH release
   c. Liver -- fatty infiltration
   d. G.I. tract -- increase flow of saliva and gastric juices -- at high concentrations causes GI irritation
   e. CV system -- peripheral vasodilitation
   f. Hypoglycemia
   g. Pancreas
   h. Sexual
2. Blood levels
   a. Legal limit for operation of motor vehicle = 0.10% (w/v)
      1) 100 lb person, 3 beers
      2) 200 lb person, 6 beers
   b. 0.3-0.4% stupor or coma
   c. 0.5% often fatal
3. Distribution -- body water
   a. Air/blood, 0.05% (2000 ml air = 1 ml blood)
4. Biotransformation (90-98%)
   a. Pathway



b. Blood level decrease 0.016%/hr

5. Chronic effects

a. Liver

1. Fatty liver

2. Alcoholic hepatitis -- 30% of alcoholics

3. Cirrhosis

a) 50% of cirrhosis is associated with alcoholism

b) 7 times more frequent among alcoholics

b. "Fetal Alcohol Syndrome"

B. 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

C. Isopropanol

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

2. Toxicity

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

b. Prominent gastritis

VI. GLYCOLS

A. Ethylene glycol ($OHCH_2CH_20HH$)

1. Toxicity

a. CNS depression

b. Kidney injury - oxalate

B. Diethylene glycol ($HOCH_2CH_2OCH_2CH_2OH$)

1. Used in sulfanilamide preparation

2. Toxicity similar to ethylene glycol

C. Propylene glycol (CH_3-CHOH-CH_2OH)

1. CNS depression

2. Low toxicity

VII. GLYCOL ETHERS

A. Ethylene glycol monomethyl ether

$CH_3OCH_2CH_2OH$

B. Ethylene glycol monoethyl ether

$CH_3CH_2OCH_2CH_2OH$

1. Both produce degeneration of testicular germinal epithelium

2. Teratogenic

C. Propylene glycol monomethyl ether

1. Not a reproductive toxin

VIII. 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 laboratory animals

c. Toxicity due to a metabolite

B. Toluene ($C_6H_5CH_3$)

1. CNS depression

2. Industrial monitoring -- hippuric acid in urine

3. Relatively safe solvent

C. Styrene ($C_6H_5CH_2=CH_2$)

1. Used in production of plastics

2. Dermatitis

3. Mutagenic in some studies but noncarcinogenic

IX. OTHERS

A. Acrylonitrile ($CH_2=CHCN$)

1. Cyanide released

2. Depletes glutathione

3. CNS is major target organ but also affects liver and kidney

4. Mutagen and carcinogen

B. Carbon disulfide

1. Chronic - neuropsychiatric

C. Dioxane ($C_4H_8O_2$)

1. Respiratory irritant

2. Kidney and liver injury

3. Tumors--liver and nasal cavity

Part IIF

Principles of Risk Assessment

PRINCIPLES OF RISK ASSESSMENT

A Nontechnical Review

WORKSHOP ON RISK ASSESSMENT

United States Environmental Protection Agency

The materials presented here have been reviewed by personnel from the United States Environmental Protection Agency. They do not, however, necessarily reflect United States Environmental Protection Agency policy. The materials were prepared primarily by:

ENVIRON CORPORATION
Washington, D.C.

CONTENTS

CONTENTS (con't)

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

[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:

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

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:

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

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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.

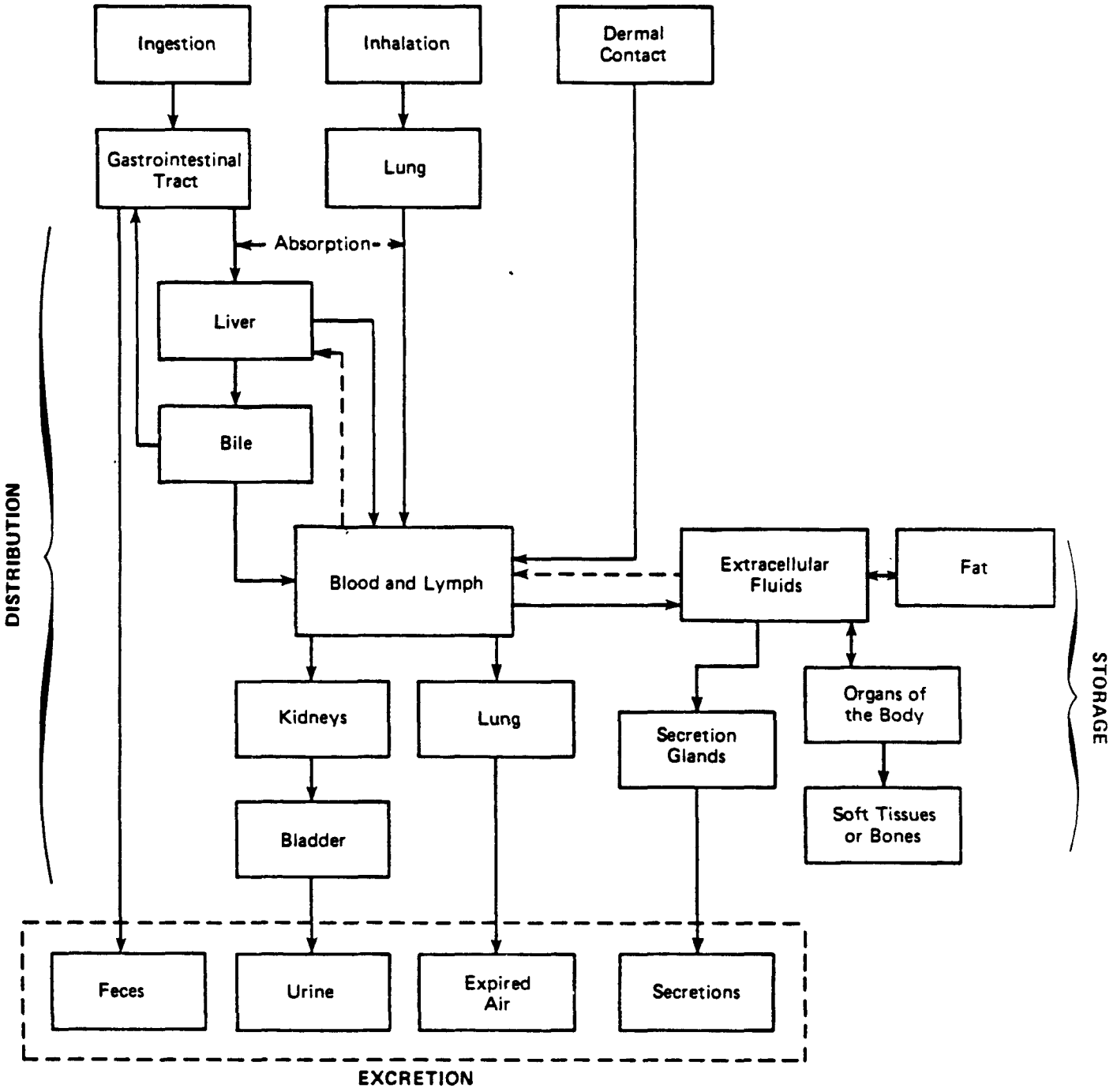
Absorption

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 containing 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 significance 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

[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:

- Milligrams per kilogram body weight per day
- Milligrams per square meter of body surface area per day
- Parts per million in the air, water, or diet
- 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 biochemical 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.

III. "Project Evaluation: Benefit-Cost Analysis"

Part IIG

Principles of Carcinogenicity

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

d. <u>In vivo</u> formation of N-nitroso compounds

a) Small amounts of nitrite and larger amount of nitrate are consumed in foods and water

b) Nitrate is absorbed in upper small intestine, excreted in saliva and reduced to nitrite by mouth bacteria

c) Nitrite is then swallowed with saliva. Therefore, nitrite may be available in stomach for

N-nitrosations (acid-catalyzed; bacterial?)

d) NH_4 may be converted to nitrite and nitrite by microorganisms in lower intestinal tract

2) Amides and amines

a) May be taken in foods and medicines

b) May be formed in tissues and GI tract from normal intermediates such as choline, amino acids, etc.

5. Symmetric dialkylhydrazines

a. Cycad nut--methylazodymethanol--glucoside (CYASIN)

6. Dioxane

7. Benzene - leukemia

8. Thioamides

a. Thioacetamide

b. Thiouracil

9. Urethane

10. Ethionine

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

12. Microbiologic carcinogens

a. Mycotoxins

Aflatoxin B_1 (B_2, G_1, G_2)

13. 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

1. Number of tumors increases

2. Time to onset decreases

B. Inducers

1. Often increase detox and decrease tumors

C. Species and strain

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

2. Age - younger more susceptible, DES transplacenta

D. Sex

1. May be promoter

E. Immunologic factors

F. Biotransformation

G. Repair

1. Lacks it

2. More susceptible

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 carcinogenenicity in humans - data in animals indicates the chemical is not carcinogenic

PART III

RISK MANAGEMENT

Part IIIA

Overview of Drinking Water Health Advisories Occurrence, Chemistry, and Treatment Technologies

Overview of Drinking Water Health Advisories

Occurrence, Chemistry, and Treatment Technologies

I. Occurrence

A. Contaminants regulated under Safe Drinking Water Act (SDWA)[1] [Figure 1]

1. Classes of contaminants not yet covered in Health Advisories

a. Microbials -- filtration and disinfection treatment required

b. Radionuclides

(1) Most are naturally-occurring alpha emitters

(2) Radon-222 (gas) [Figures 2 & 3] radionuclide found in some ground waters[2]

c. Disinfection by-products [Figure 4]

(1) Most of these will not be the subject of the same kinds of "spill" situations as synthetic organic chemicals (SOCs) and some metals

(2) Subject of long-term research

2. Corrosion by-products [Figure 5]

a. Generally are associated with the corrosion of metal pipes by low alkalinity, low pH (acidic) waters[3]

b. Other factors can be important -- temperature, electrical currents, galvanic corrosion

c. Metals -- (Cd, Pb, Zn, Cu, Sb, Sn, plus asbestos)

d. Corrected with a corrosion control program

(1) Addition of lime or other base to increase pH and alkalinity

(2) Other chemicals like phosphates and silicates may help

FIGURE 1: REGULATORY AGENDA FOR DRINKING WATER

USEPA Agenda	USEPA Target Dates	Congressional Deadlines	Congressional Requirements
Phase I	June 1987	June 1987	9 standards
Trichloroethylene			
Carbon tetrachloride			
1,1,1-Trichloroethane			
1,2-Dichloroethane			
Vinyl chloride			
Benzene			
Dichlorobenzene			
1,1-Dichloroethylene			
Fluoride			
Phase IA	June 1988	June 1988	40 standards
Tetrachloroethylene			
Phase II			
Total coliforms			
Giardia lamblia			
Turbidity			
Viruses			
Required filtration for surface water systems		(December 1987)	Mandatory filtration
Inorganics			
Arsenic			
Asbestos			
Barium			
Cadmium			
Chromium			
Copper			
Lead			
Mercury			
Nitrate			
Selenium			
Nitrite*			

*Contaminants substituted for seven listed in the congressional conference report

FIGURE 1 (Continued): REGULATORY AGENDA FOR DRINKING WATER

USEPA Agenda	USEPA Target Dates	Congressional Deadlines	Congressional Requirements
Organics			
Lindane			
Methoxychlor			
Toxaphene			
2,4-D			
2,4,5-TP			
Aldicarb			
Chlordane			
Carbofuran			
Alachlor			
Epichlorohydrin			
Toluene			
Ethyl benzene*			
Heptachlor*			
PCBs			
Acrylamide			
Dibromochloropropane (DBCP)			
1,2-Dichloropropane			
Pentachlorophenol			
Ethylene dibromide			
Xylene			
trans-1,2-Dichloroethylene			
cis-1,2-Dichloroethylene			
ortho-Dichlorobenzene			
Chlorobenzene			
Heptachlor epoxide*			
Styrene*			

*Contaminants substituted for seven listed in the congressional conference report

FIGURE 1 (Continued): REGULATORY AGENDA FOR DRINKING WATER

USEPA Agenda	USEPA Target Dates	Congressional Deadlines	Congressional Requirements
Phase III	October 1988	June 1989	35 standards
Radium 226 and 228			
Beta particle and photon radioactivity			
Uranium			
Gross alpha particle activity			
Radon			
Phase IV	September 1990		
Required disinfection			Mandatory disinfection
Chlorine and by-products			
Chlorine dioxide and by-products			
Chlorinated acids, haloalcohols and haloaldehydes			
Iodine and by-products			
Ozone			
High pH			
Silver			
Ferrate			
Chloramines and ammonia			
Chlorophenols			
Trihalomethanes			
Acetonitriles			
Bromine and by-products			
Potassium permanganate			
Ionizing radiation			
UV light			

*Contaminants substituted for seven listed in the congressional conference report

FIGURE 1 (Continued): REGULATORY AGENDA FOR DRINKING WATER

USEPA Agenda	USEPA Target Dates	Congressional Deadlines	Congressional Requirements
Phase V		June 1989	
Inorganics			
Molybdenum			
Sulfate			
Antimony			
Vanadium			
Nickel			
Thallium			
Cyanide			
Organics			
Dalapon			
Diquat			
Endothall			
Glyphosate			
Adipates			
2,3,7,8-TCDD (Dioxin)			
Dibromomethane			
Hexachlorocyclopentadiene			
Methylene chloride*			
1,1,2-Trichloroethane			
Vydate			
Simazine			
PAHs			
Atrazine			
Phthalates			
Pichloram			
Dinoseb			

*Contaminants substituted for seven listed in the congressional conference report

FIGURE 2: ^{226}Ra DECAY CHAIN CHARACTERISTICS

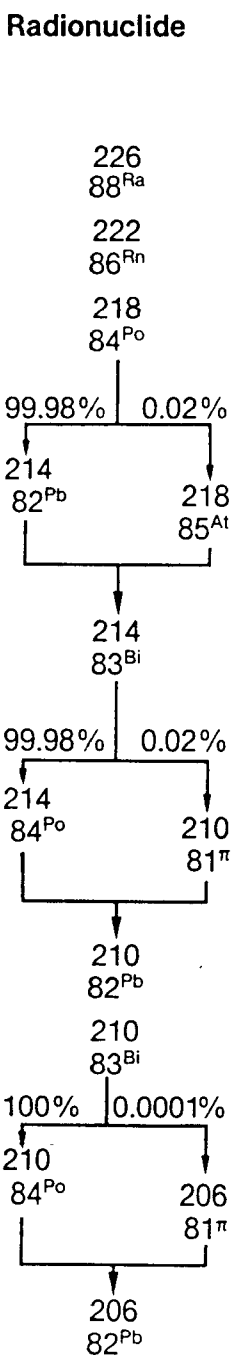


FIGURE 3: GEOMETRIC AVERAGE RADON CONCENTRATION IN PUBLIC GROUNDWATER SUPPLIES (pCi/L)

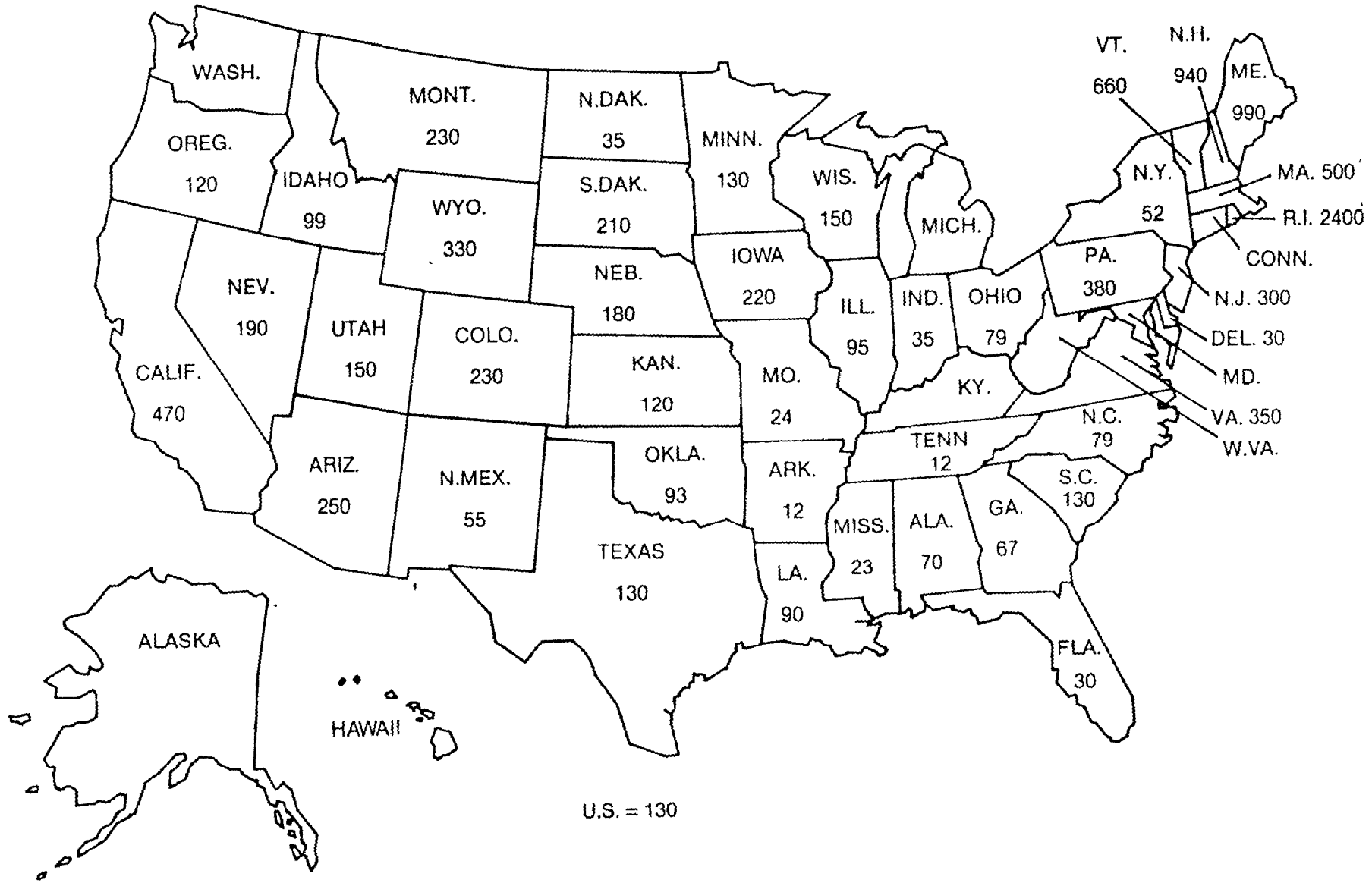
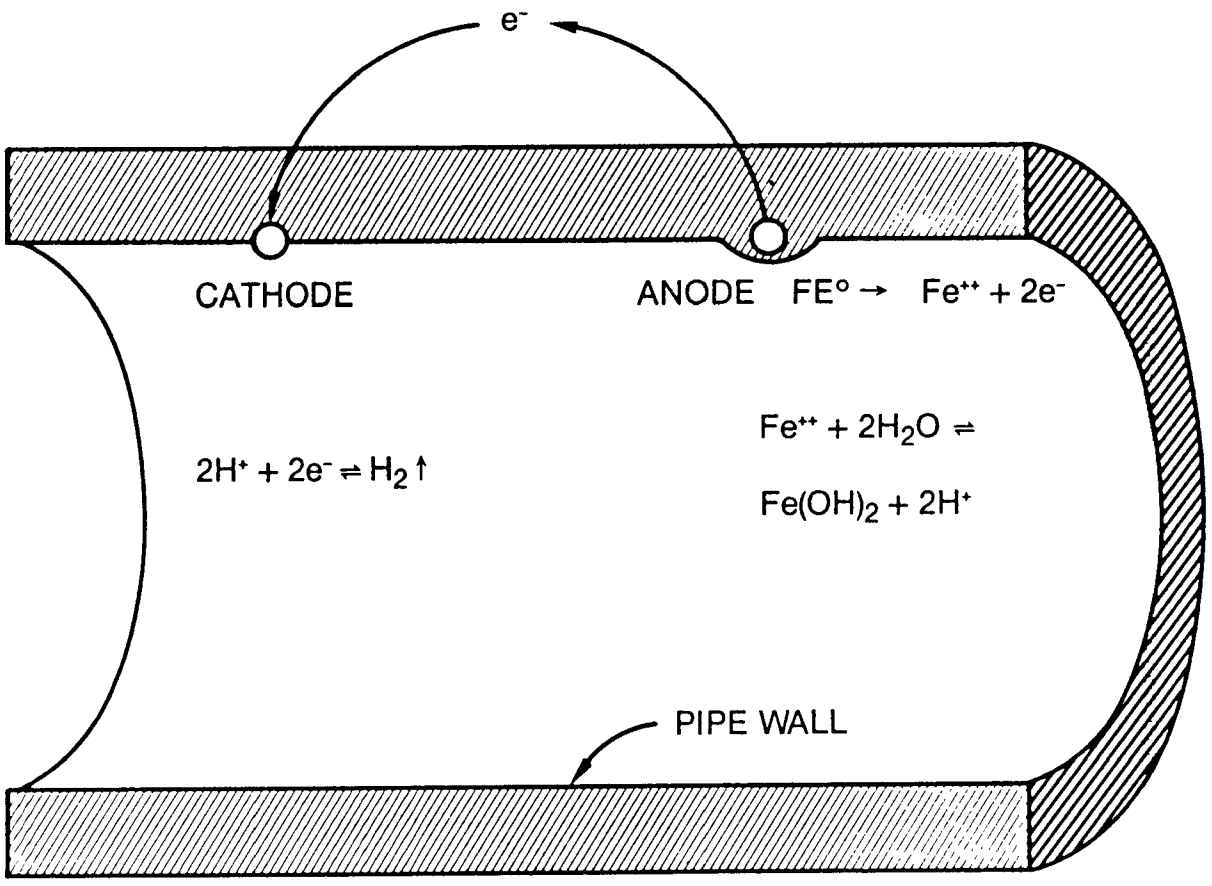


FIGURE 4: SOME DISINFECTION BY-PRODUCTS UNDER CONSIDERATION

CRITERIA DOCUMENT/ COMPOUND	Health Advisories				cancer risk	10-cities survey	90-day requested
	1-day	10-day	Longer term	Life time			
HALOACIDS, HALOALCOHOLS, HALOALDEHYDES and HALOKETONES							
monochloroacetic acid	X	X	NE	X	X	P	X
dichloroacetic acid			NE		C	P	X
trichloroacetic acid			NE	X	C	P	X
trichloroethanol	X	X	NE	X	X		
chloroacetaldehyde	X	X	NE	X	X		
dichloroacetaldehyde	X	X	NE	X	X		
trichloroacetaldehyde			NE		X	P	X
1,1,dichloropropanone			NE	X	X		
1,3-dichloropropanone	X	X	NE	X	X		
1,1,1-trichloropropanone	X	X	NE	X	X	P	X
1,1,1,3-tetrachloropropanone			NE	X	X		
CHLORINE DIOXIDE, CHLORITE, and CHLORATE							
chlorine dioxide			NE		X		
chlorite			NE		X		
chlorate			NE		X		
CHLOROPHENOLS							
2-monochlorophenol	X	X	NE		X		
2,4-dichlorophenol	X	X	NE		C		
2,6-dichlorophenol	X	X	NE	X	X		
2,4,6-trichlorophenol	X	X	NE	X			X
HALOACETONITRILES, CHLOROPICRIN and CYANOGEN CHLORIDE							
bromochloroacetonitrile	X	X	NE	X		P	
dichloroacetonitrile			NE			P	
dibromoacetonitrile			NE			P	
chloropicrin	X	X	NE	X	X	P	X
cyanogen chloride	X	X	NE	X	X	P	
TRIHALOMETHANES							
chloroform			NE			P	
bromoform			NE		I	P	
bromodichloromethane			NE		I	P	
dibromochloromethane			NE		I	P	
CHLORAMINES and AMMONIA							
chloramine			NE		I	P	X

I = study in progress
X = data not available to determine
NE = not evaluated
C = data suggest possible carcinogenicity
P = present

FIGURE 5: CORROSION



Galvanic series — Order of activity of common metals used in water distribution systems

Metal	Activity
Zinc	More active
Mild steel	↑
Cast iron	|
Lead	|
Brass	|
Copper	|
Stainless steel	Less active

(3) Materials --

a) Lead ban

b) Coatings

c) Cathodic protection

3. Volatile Synthetic Organic Chemicals (VOCs)

a. Industrial solvent [Figure 6] production scheme[4]

b. Used for paint stripping metal degreasing

c. Vinyl chloride or "How do we spill a gas into ground water?" [Figure 7] -- biodegradation [5]

d. Rank order of occurrence [figure 8] -- CERCLA (Superfund) and RCRA Sites

4. Synthetic Organic Chemicals (SOCs)

a. Additives

(1) Direct -- acrylamide and epichlorohydrin monomers (contaminants in polymer coagulants)

(2) Indirect -- coatings

a) Coal tar -- polyaromatic hydrocarbons (PAHs)

b) Paint solvents -- tetrachloroethylene, toluene, xylenes, etc.

c) Pentachlorophenol -- wood preservative

b. Pesticides

(1) Generally found in agricultural areas

(2) Ground water -- aldicarb plus breakdown products sulfoxide and sulfone from Long Island potato fields

FIGURE 6: SIMPLIFIED MANUFACTURING SCHEME FOR INDUSTRIAL SOLVENTS

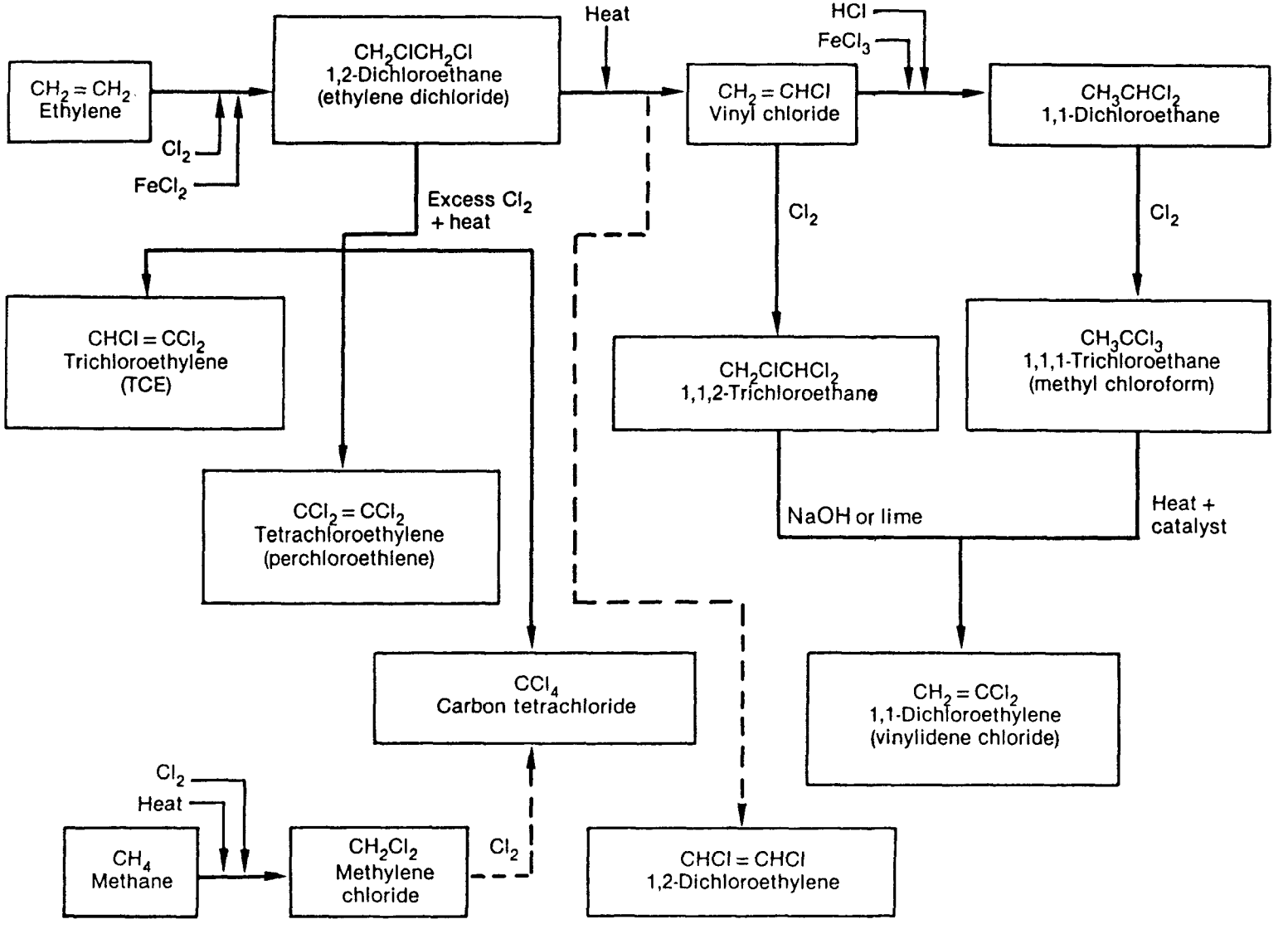


FIGURE 7: DEGRADATION OF UNSATURATED CHLORINATED ETHANES

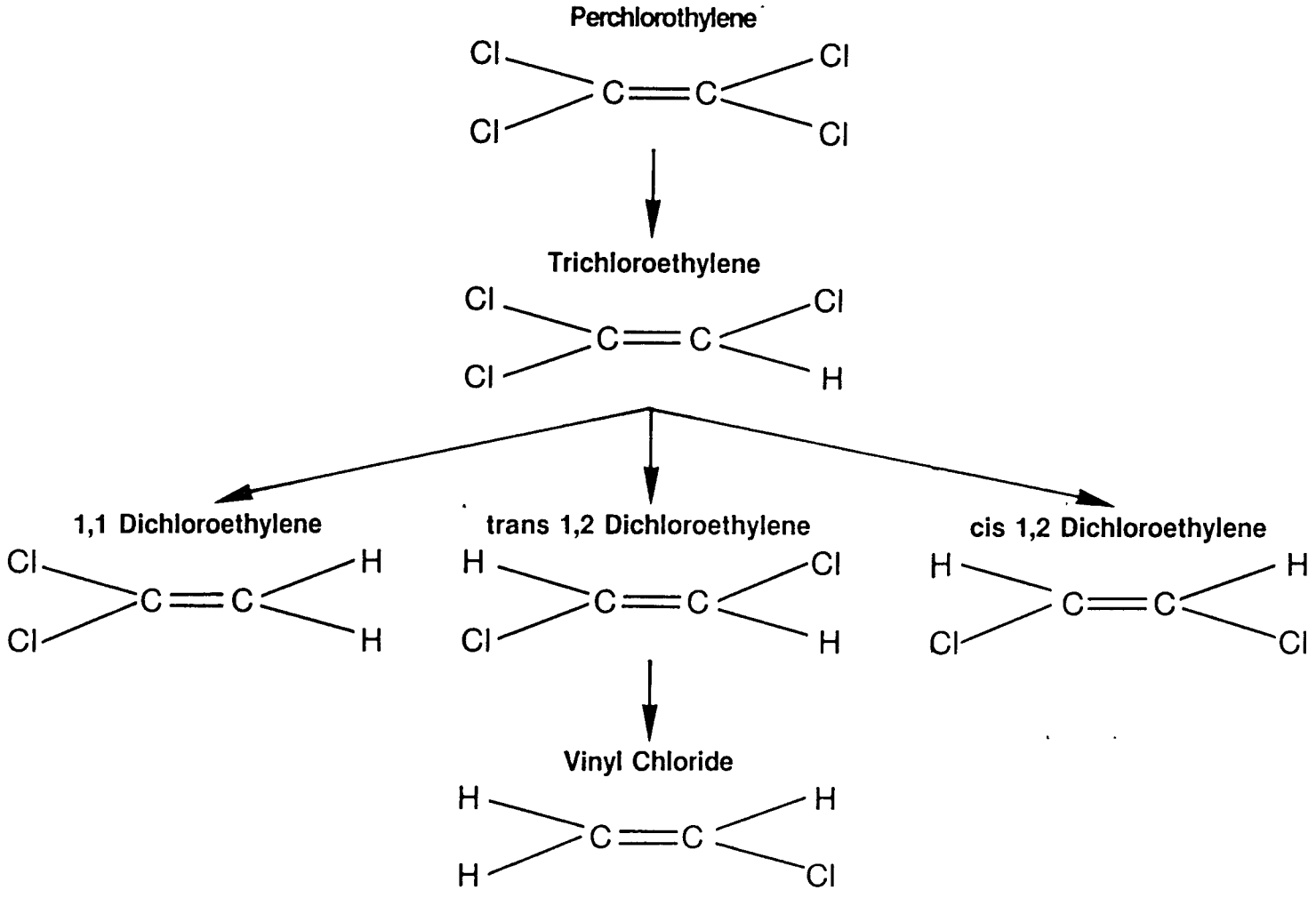


FIGURE 8: RANK ORDER OF CHEMICALS DETECTED IN GROUND WATER AT RCRA AND CERCLA SITES (EMSL, 1985)

RANK	NUMBER OF SITES POSITIVE	% OF SITES POSITIVE	CHEMICAL NAME	CHEMICAL TYPE*
1	63	43.2	TRICHLOROETHENE (-ETHYLENE), TCE	V
2	57	39.0	METHYLENE CHLORIDE	V
3	57	39.0	TETRACHLOROETHENE (PCE) (-YLENE)	V
4	57	39.0	TOLUENE	V
5	52	35.6	1,1-DICHLOROETHANE	V
6	52	40.0	BIS(2-ETHYLHEXYL) PHTHALATE	B
7	50	34.2	BENZENE	V
8	50	34.2	1,2-TRANS-DICHLOROETHENE	V
9	49	33.6	1,1,1-TRICHLOROETHANE	V
10	46	31.5	CHLOROFORM (TRICHLOROMETHANE)	V
11	46	21.5	ETHYL BENZENE	V
12	39	26.7	1,2-DICHLOROETHANE	V
13	37	25.3	1,1-DICHLOROETHENE	V
14	35	27.1	PHENOL	A
15	30	20.0	VINYL CHLORIDE	V
16	30	20.5	CHLOROBENZENE	V
17	28	21.5	DI-N-BUTYL PHTHALATE	B
18	23	18.7	NAPHTHALENE	B
19	23	15.8	CHLOROETHANE	V
20	22		ACETONE	V

* V = volatile organic chemical A = acid extractable compound
B = base neutral compound P = pesticides

FIGURE 8 (Continued): RANK ORDER OF CHEMICALS DETECTED IN GROUND WATER AT RCRA AND CERCLA SITES (EMSL, 1985)

RANK	NUMBER OF SITES POSITIVE	% OF SITES POSITIVE	CHEMICAL NAME	CHEMICAL TYPE*
21	20	15.5	PENTACHLOROPHENOL	A
22	20	14.2	BHC-GAMMA (LINDANE)	P
23	17	11.6	CARBON TETRACHLORIDE (TETRACHLOROMETHANE)	V
24	17	11.6	1,1,2,2-TETRACHLOROETHANE	V
25	16	11.0	1,1,2-TRICHLOROETHANE	V
26	16	11.0	FLUOROTRICHLOROMETHANE	V
27	15	11.5	DIETHYL PHTHALATE	B
28	14	10.8	BUTYL BENZYL PHTHALATE	B
29	14	10.8	1,2-DICHLOROBENZENE	B
30	14	10.9	2,4-DIMETHYLPHENOL	A
31	13	8.9	1,2-DICHLOROPROPANE	V
32	13	8.9	CHLOROMETHANE (METHYL CHLORIDE)	V
33	12	9.2	DI-N-OCTYL PHTHALATE	B
34	12	8.5	BHC-ALPHA	P
35	11	7.8	HEPTACHLOR	P
36	10	7.1	DIELDRIN	P
37	10	7.1	ENDRIN	P
38	10	7.1	BHC-BETA	P
39	10	7.1	BHC-DELTA	P

* V = volatile organic chemical A = acid extractable compound
B = base neutral compound P = pesticides

(3) Surface water -- alachlor from corn fields in Tiffin, Ohio water

(4) More difficult to measure than VOCs, so less data are available

c. Industrial chemicals

(1) Polychlorinated biphenyls (PCBs)

a) Transformers and capacitors

b) 110v submersible well pump capacitors in Region V found to contain PCB oil (Figure 9)

(2) Combustion products

a) Polyaromatic hydrocarbons (PAHs)

b) Dioxins

d. Inorganic Chemicals (IOCs)

(1) Generally found in well water

(2) Generally due to mineral formations

(3) Concentrations do not vary as much as SOCs

(4) Some surface waters may contain asbestos -- mine tailings or natural erosion

(5) Nitrates

a) Wastewater (septic tanks)

b) Fertilizer

B. Other contaminants for which Health Advisories exist or are contemplated

1. Pesticide survey [Figure 10]

a. Ground water

b. Tend to be more water soluble compounds

FIGURE 9: VIEW OF SUBMERSIBLE PUMP

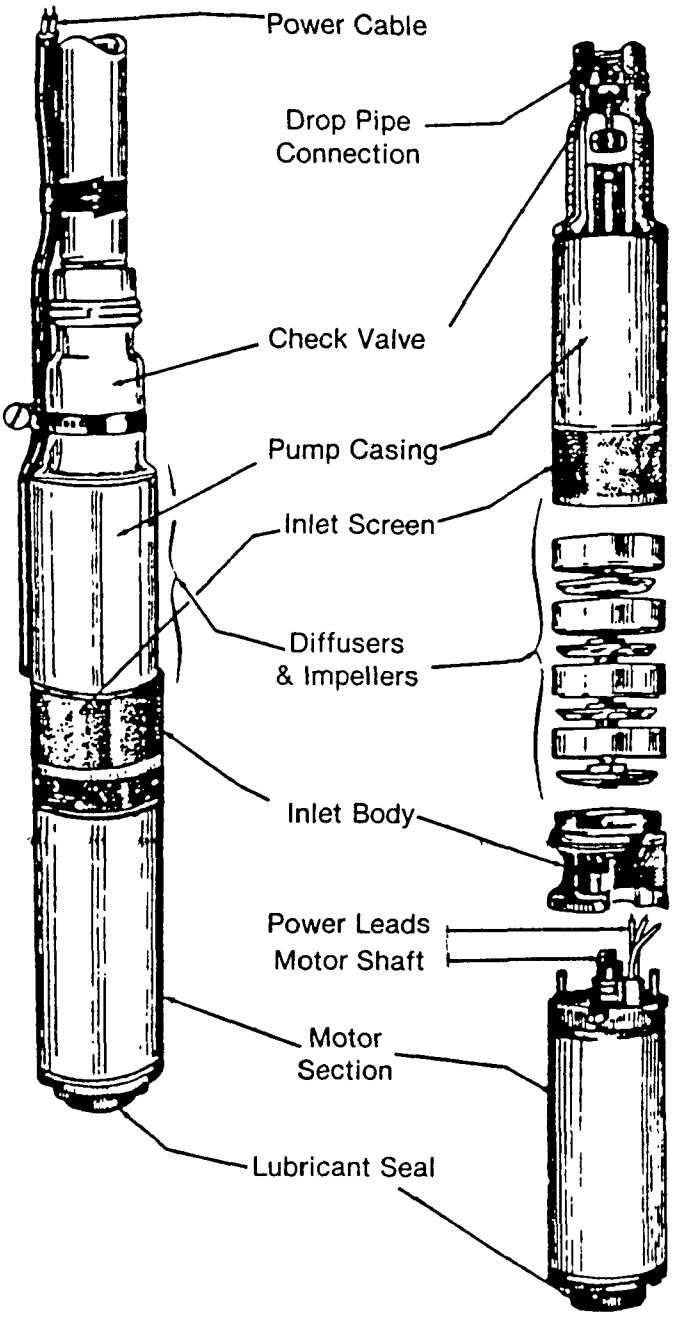


FIGURE 10: TENTATIVE LIST OF ANALYTES FOR THE NATIONAL PESTICIDES SURVEY

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

c. A number of methods are under development to cover these compounds

2. 1445 monitoring

a. VOCs [Figure 11]

b. Plus pesticide survey list [Figure 10]

II. Analytical Methods

A. Sampling procedures

1. Bottles and instruction should be provided by labs

2. Problems

a. Adsorption to container

(1) Acids for metals

(2) Solvents for some SOCs

b. Volatile Organic Chemicals (VOCs)

(1) Carefully fill bottle

(2) No air space (as indicated by lab)

(3) Seal container tightly

c. Sunlight can break down a number of VOCs and SOCs -- ultraviolet light attacks double bonds

d. Reducing agents are used to stop TTHM reaction -- may interfere with other DBP's

e. Corrosion by-products -- time function

B. Analytical Procedures

1. Inorganic Chemicals (IOCs)

a. Wet chemistry -- colorimetric

b. Atomic adsorption metals

c. Specific ion probes -- nitrate, fluoride, etc.

FIGURE 11: TENTATIVE LIST OF HEALTH ADVISORIES FOR UNREGULATED VOCs UNDER SECTION 1445

Chloroform
Bromodichloromethane
Chlorodibromomethane
Bromoform
trans-1,2-Dichloroethylene
Chlorobenzene
m-Dichlorobenzene
Dichloromethane
cis-1,2-Dichloroethylene
o-Dichlorobenzene
1,2,4-Trichlorobenzene
Fluorotrichloromethane
Dichlorodifluoromethane
Dibromomethane
1,2-Dibromo-3-chloropropane
Toluene
p-Xylene
o-Xylene
m-Xylene
1,1-Dichloroethane
1,2-Dichloropropane
1,1,2,2-Tetrachloroethane
Ethylbenzene
1,3-Dichloropropane
Styrene

Chloromethane
Bromomethane
Bromochloromethane
1,2,3-Trichloropropane
1,2,3-Trichlorobenzene
n-Propylbenzene
1,1,1,2-Tetrachloroethane
Chloroethane
1,1,2-Trichloroethane
Pentachloroethane
bis-2-Chloroisopropyl ether
sec-Dichloropropane
1,2,4-Trimethylbenzene
n-Butylbenzene
Naphthalene
hexachlorobutadiene
o-Chlorotoluene
p-Chlorotoluene
1,3,5-Trimethylbenzene
p-Cymene
1,1-Dichloropropane
iso-Propylbenzene
tert-Butylbenzene
sec-Butylbenzene
Bromobenzene

2. Organics (gas chromatography) [Figures 12 & 13]

   a. VOCs -- purge and trap

      (1) Carrier is gas (nitrogen or helium)

      (2) Solid surface for adsorption or solid support partitioning

   b. SOCs

      (1) LLE (liquid-liquid extraction)

      (2) CLS (closed loop stripping)

3. Organics [HPLC -- high performance (pressure) liquid chromatography]

   a. Carrier is solvent under high pressure

   b. Solid surfaces are also used for adsorption or partitioning

   c. Used for carbamate and chlorophenoxy herbicides that breakdown when heated

C. Numbers -- goals, detection, quantification, etc.

1. Maximum contaminant level goals are zero for Class A & B carcinogens

2. Zero can not be measured

3. Detection -- blip on the chart

4. Quantification -- a number obtained via relative response ratio (for GC) to an internal standard

   a. Generally 5 to 10 times the method detection limit (MDL)

   b. Subject to measurement error

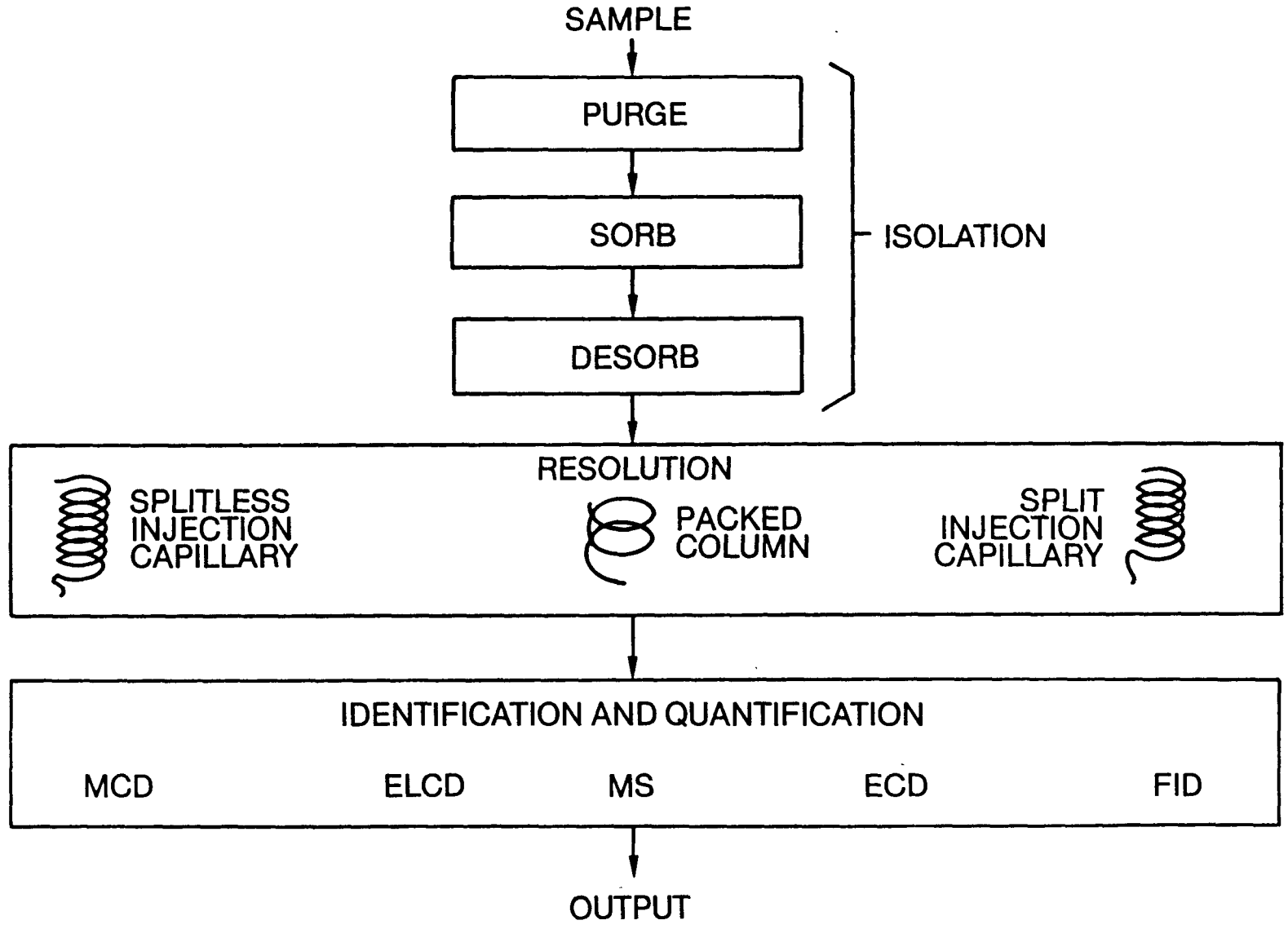
      (1) Same sample, same lab

      (2) Same sample, different labs

   c) Cannot quantitate sampling error

   d) Example, vinyl chloride

FIGURE 12: FLOWCHART OF PURGE-AND-TRAP PROCEDURE



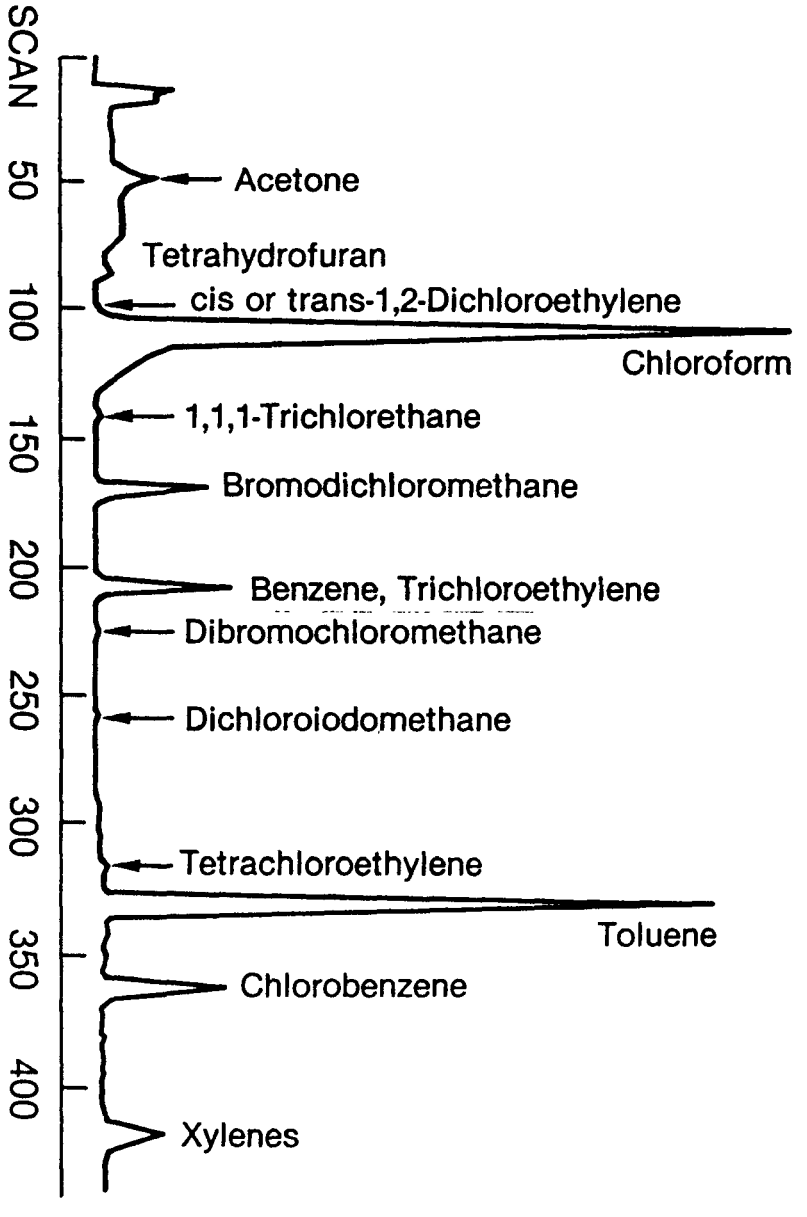


FIGURE 13: TYPICAL GC/MS CHROMATOGRAM FROM A PURGE-AND-TRAP SEPARATION

(1) ±40% at 1.5ug/L (multi-lab variation)

(2) 10^{-6} cancer risk number is 0.15ug/L.

5. Resampling positive findings

a. The VOCs have shown a wide range of variability[7] in concentration over time [Figure 14]

b. VOCs more often occur in mixtures[8] than alone [Figure 15]

c. Naturally occurring minerals tend to be more constant in concentration over time

III. Treatment Technologies

A. Non-treatment alternatives

1. Regional water supply extension

a. Dependent on geography

b. Also politics and cost

2. Alternate source -- drill a new well

3. Pump well to waste

4. Bottled water -- interim solution to reduce risk

B. Inorganic Chemical (IOC) treatment

1. Conventional treatment -- (schematics)[9]

a. Coagulation/filtration [Figure 16]

b. Lime softening [Figure 17]

c. Ion exchange softening [Figure 18]

d. Iron removal [Figure 19]

2. Removal rates vary[10] [Figures 20-21] and may depend on pH, coagulant chemical, and many other factors

3. Advanced treatment

a. Activated alumina or bone char adsorption for fluoride[11] [Figure 22]

FIGURE 14: VARIATION OF VOC CONCENTRATION WITH TIME

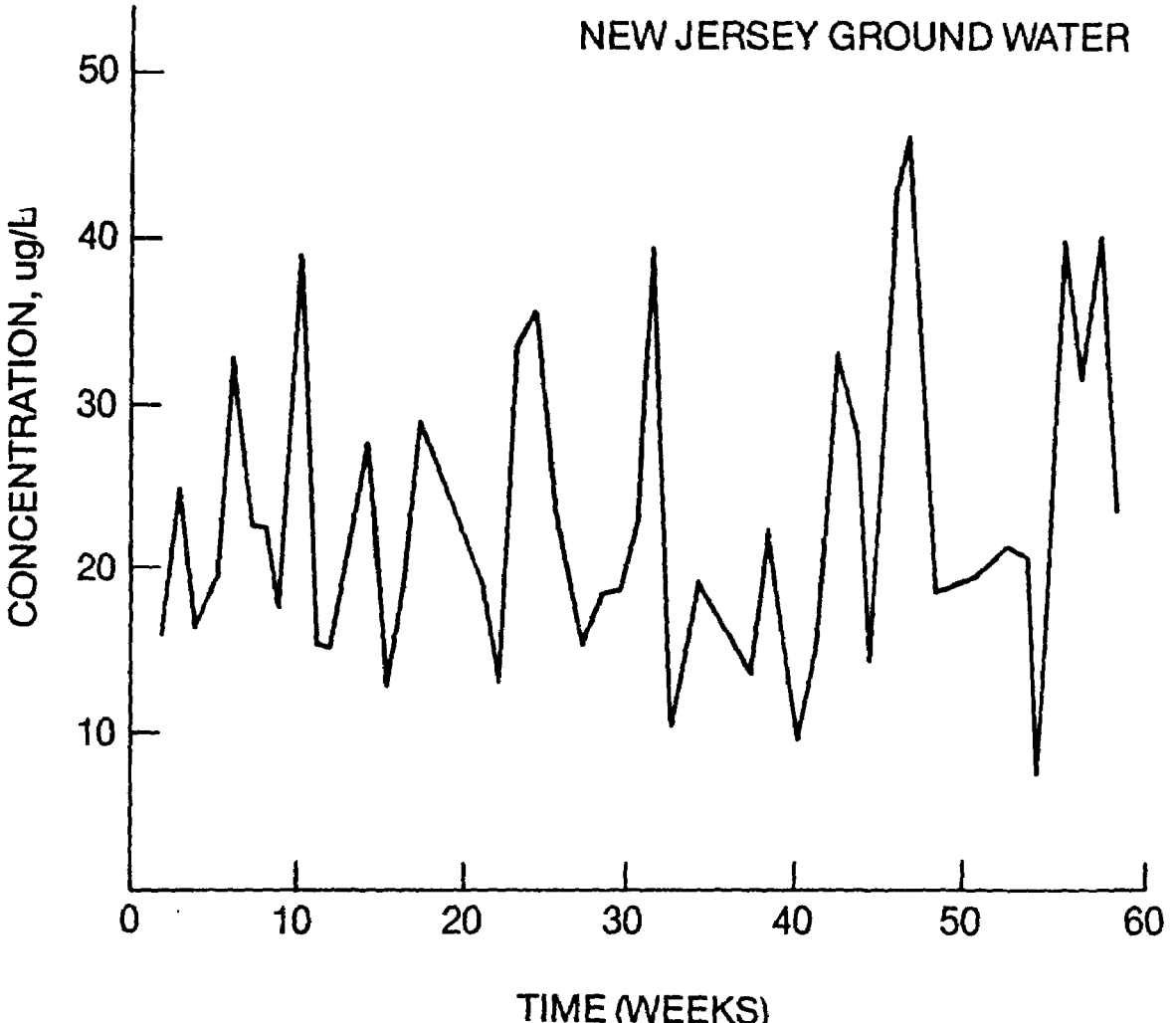


FIGURE 15: CO-OCCURRENCE OF VOCs FOR THE GROUND WATER SUPPLY SURVEY (1980-1)

	vinyl chloride	1,2-dichloroethane	1,2-dichloropropane	1,1-dichloroethylene	carbon tetrachloride	1,1-dichloroethane	cis/trans-1,2-dichloroethylene	1,1,1-trichloroethane	tetrachloroethylene	trichloroethylene	no other VOC
vinyl chloride	7	1	0	4	1	5	7	3	1	6	0
1,2-dichloroethane		10	1	3	5	1	2	2	3	3	2
1,2-dichloropropane			13	1	0	2	3	3	1	3	8
1,1-dichloroethylene				24	3	17	11	16	7	17	0
carbon tetrachloride					30	2	4	4	7	6	17
1,1-dichloroethane						41	21	28	16	26	3
cis/trans-1,2-dichloroethylene							54	23	23	45	5
1,1,1-trichloroethane								78	35	45	19
tetrachloroethylene									79	39	27
trichloroethylene										91	12

FIGURE 16: SCHEMATIC OF COAGULATION/FILTRATION PROCESSES

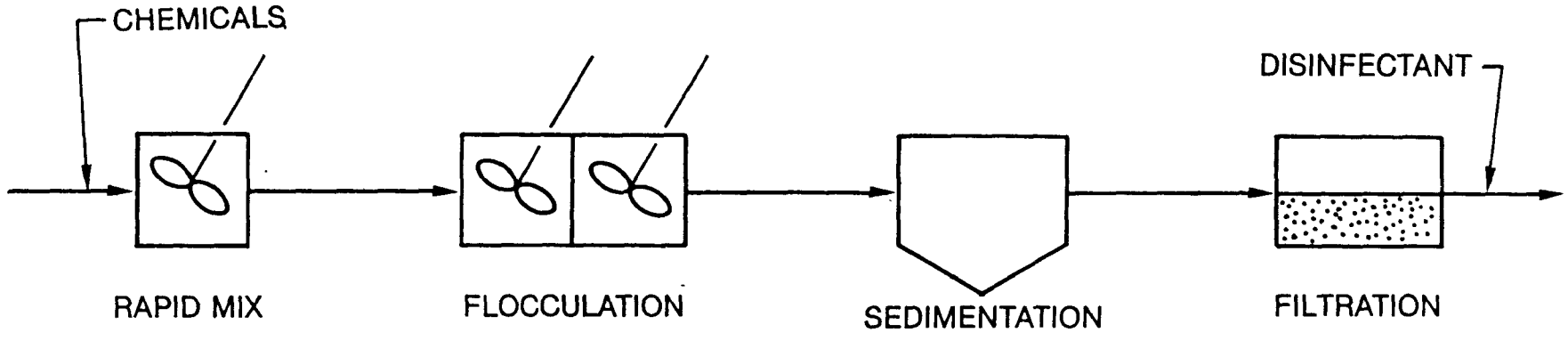


FIGURE 17: SCHEMATIC OF LIME SOFTENING PROCESSES

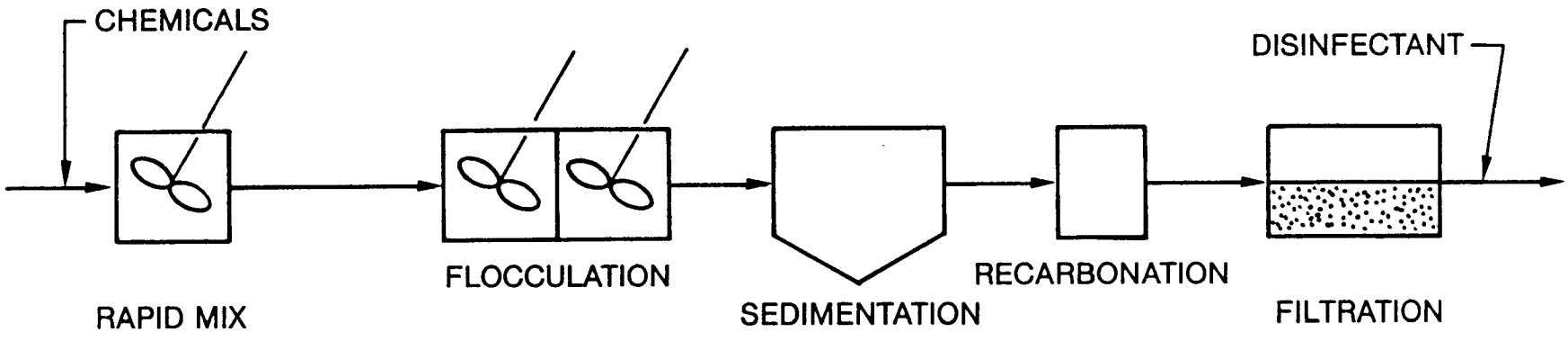


FIGURE 18: SCHEMATIC OF ION EXCHANGE SOFTENING PROCESS

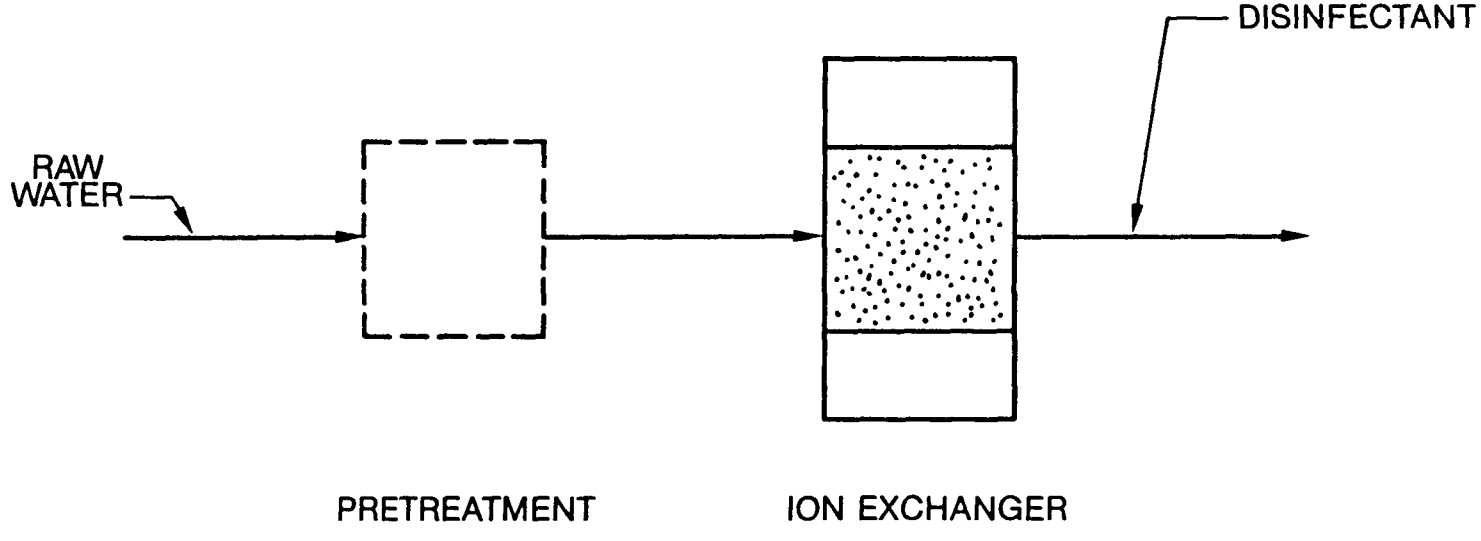


FIGURE 19: SCHEMATIC OF IRON REMOVAL PROCESS

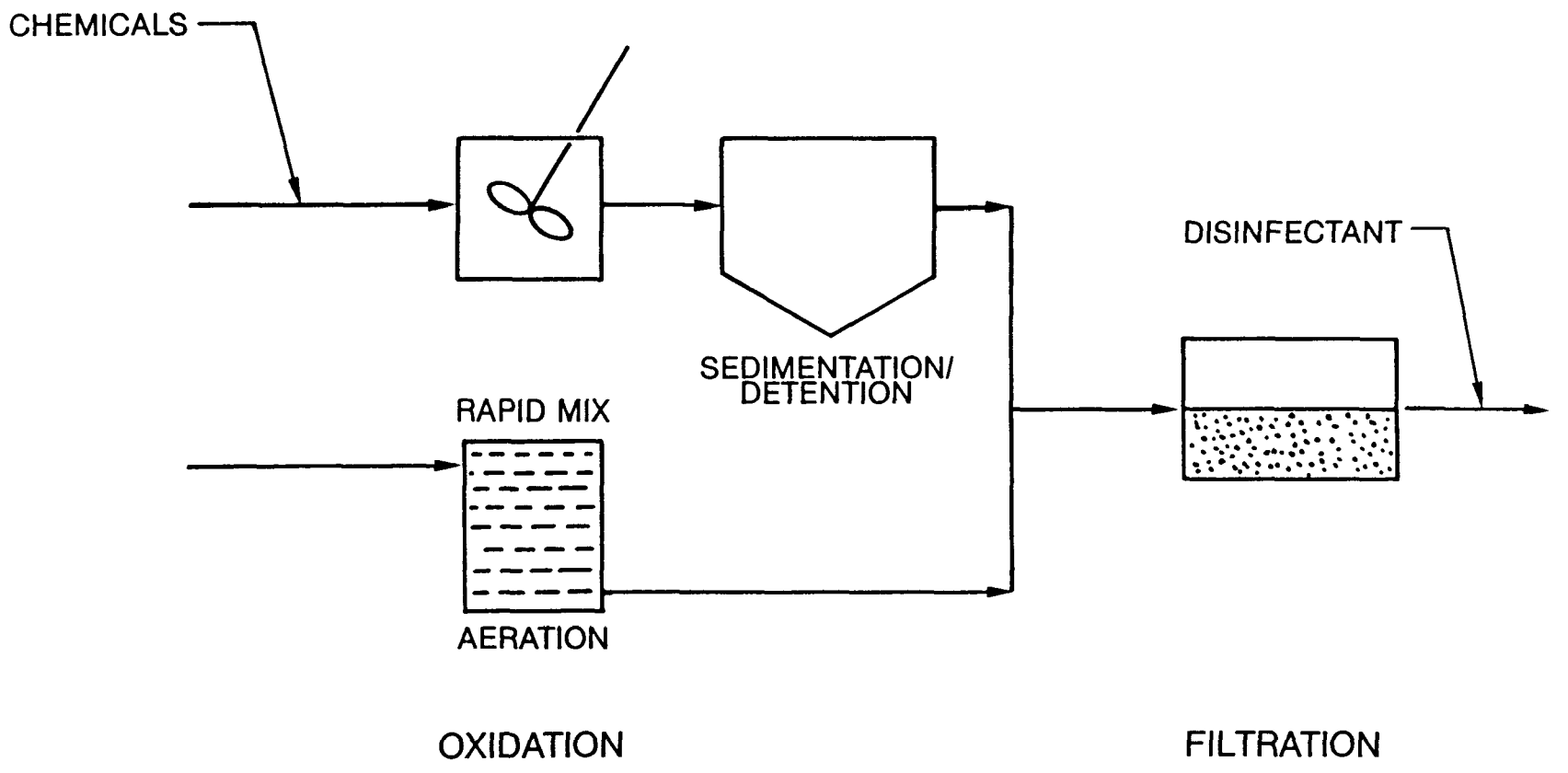


FIGURE 20: REMOVAL OF INORGANIC CONTAMINANTS BY ALUM COAGULATION

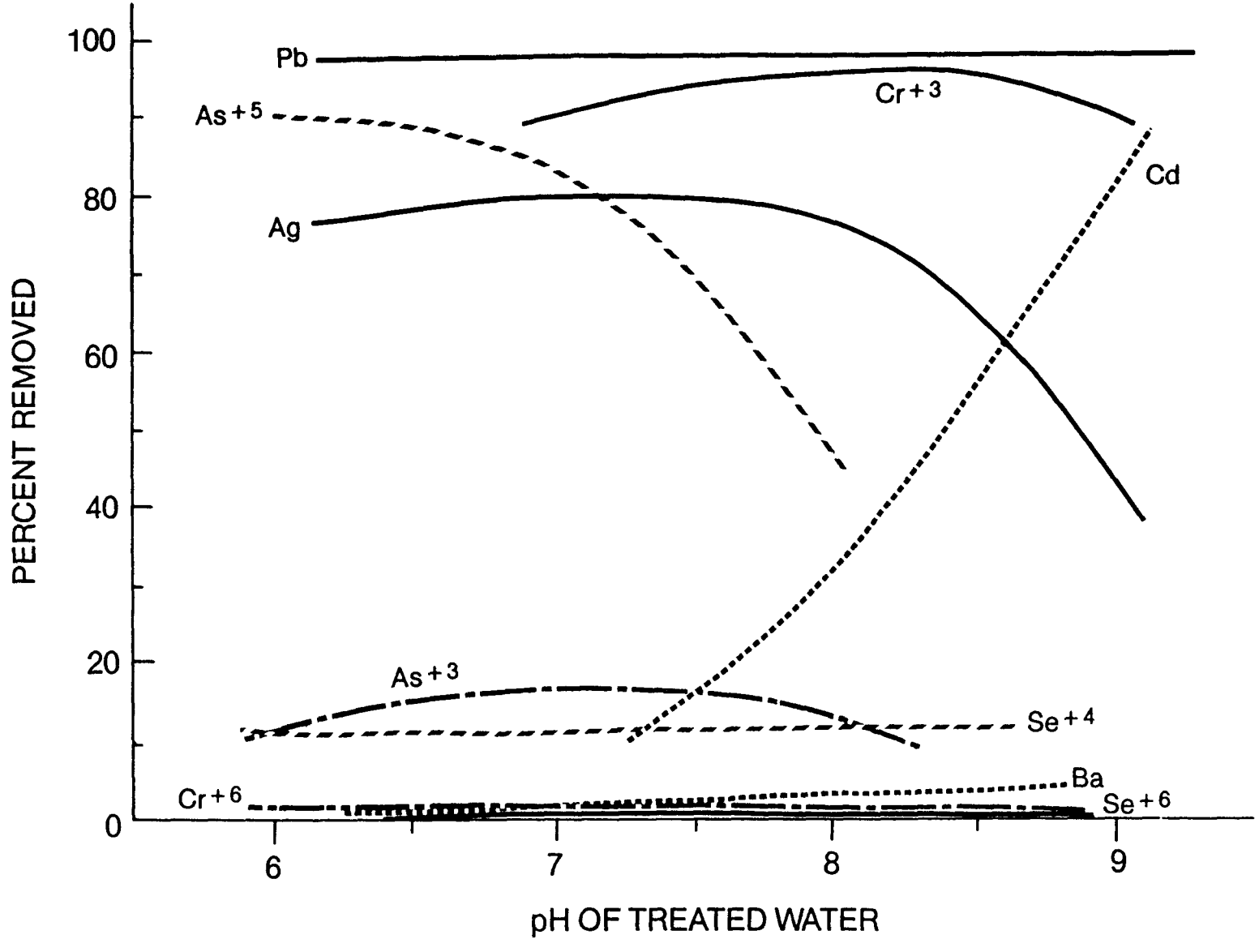


FIGURE 21: REMOVAL OF INORGANIC CONTAMINANTS BY LIME SOFTENING

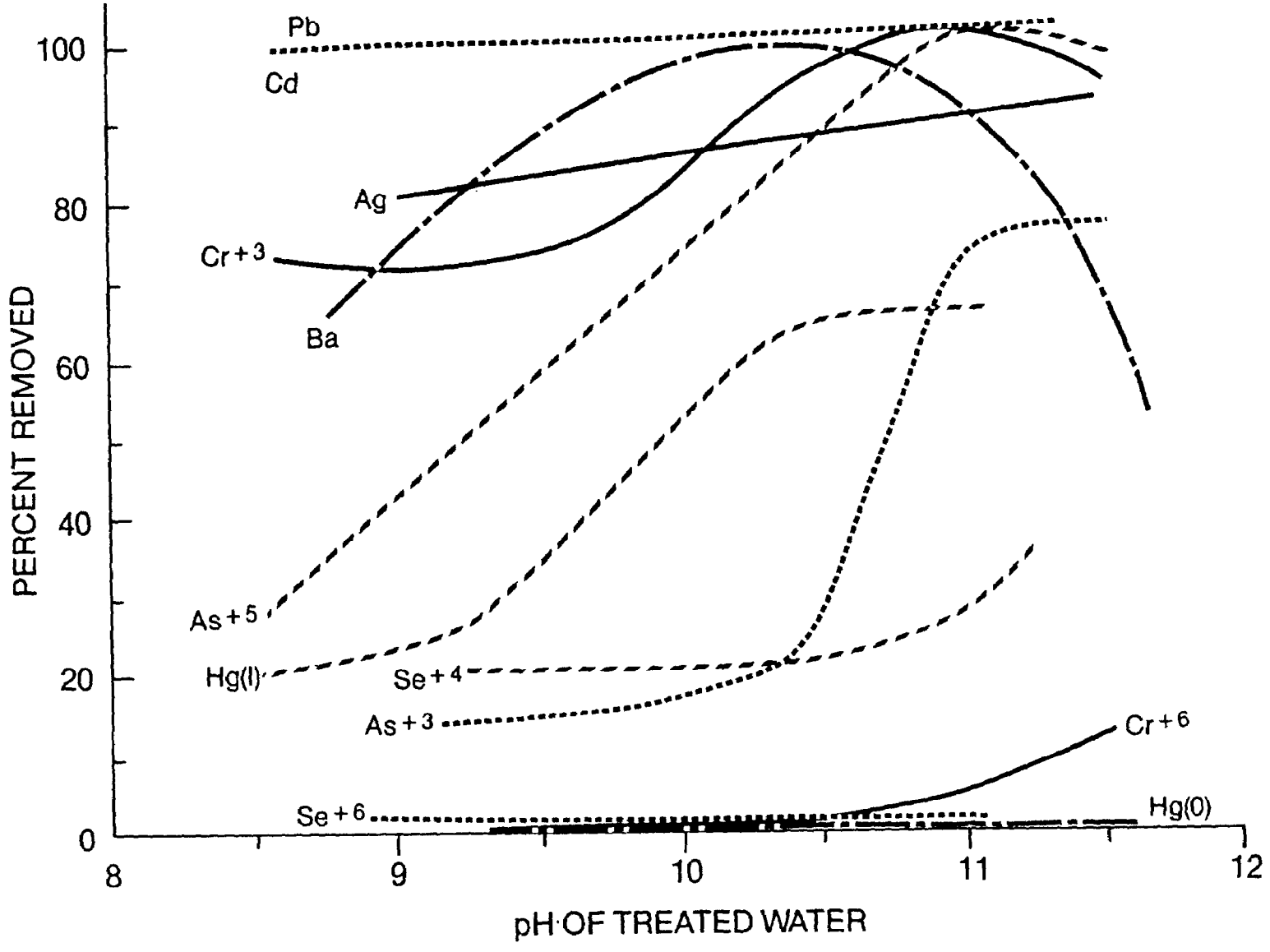
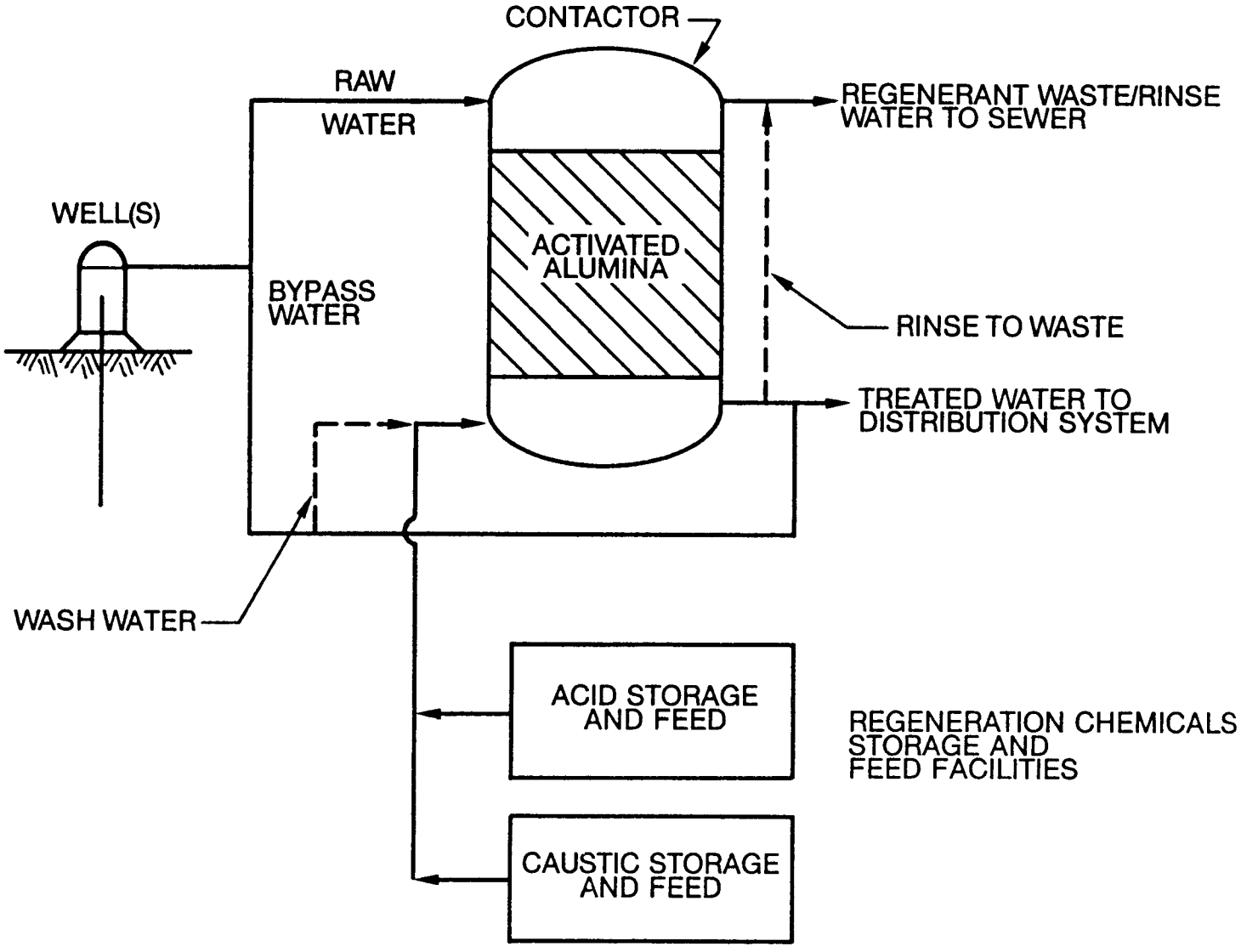


FIGURE 22: SCHEMATIC OF ACTIVATED ALUMINA PROCESS



b. Anion exchange for nitrates[12] [Figure 23]

c. Reverse osmosis -- desalting using pressure and membranes [Figure 24]

d. Electrodialysis -- desalting using direct current electricity and membranes [Figure 25]

C. SOC treatment

1. Aeration

a. Transfer to air phase by intimate mixing of air and water

b. VOCs -- low solubility plus high vapor pressure

c. Henry's Constant:

$$H = \frac{P_v}{S} \qquad \left[\frac{Atm\text{-}m^3}{mole}\right]$$

where, P_v = vapor pressure, (atm)

S = solubility, (moles/m^3)

d. Packed tower[13] is the most efficient (cost-effective) system [Figure 26]

2. Adsorption (Granular Activated Carbon, GAC)

a. Transfer to solid phase due to relatively low water solubility and higher affinity of solute for the carbon

b. Occurs in a fixed bed[15] [Figure 27]

c. Suitable for most VOCs (except vinyl chloride)

(1) Adsorption capacity measured by isotherms

(2) Design based on bench or pilot studies

(3) Trade-offs between GAC absorption versus aeration

a) Aeration and air pollution

b) GAC -- reactivation, control of microbes

FIGURE 23: SCHEMATIC OF ION EXCHANGE PROCESS

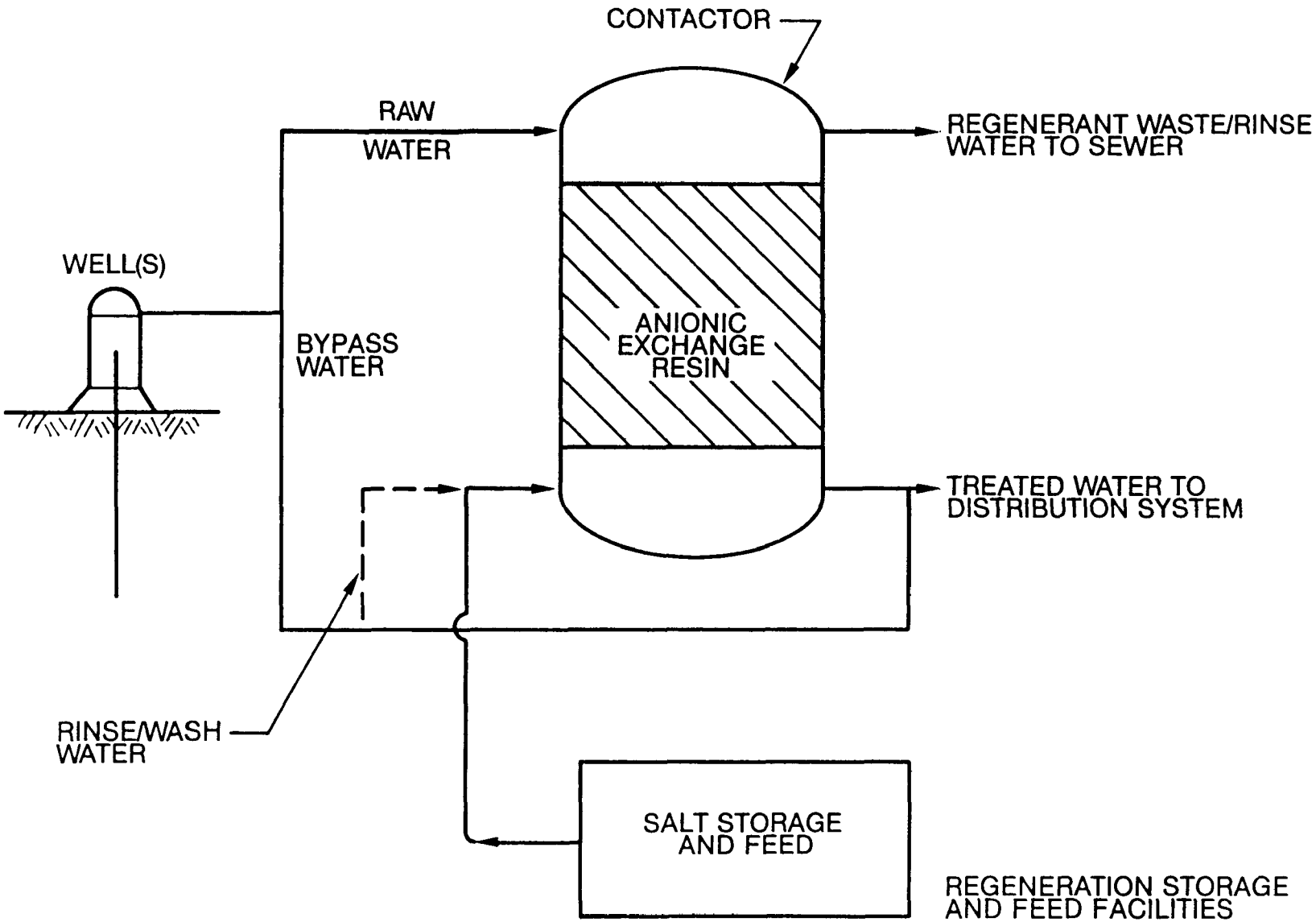


FIGURE 24: TYPICAL REVERSE OSMOSIS TREATMENT FACILITY

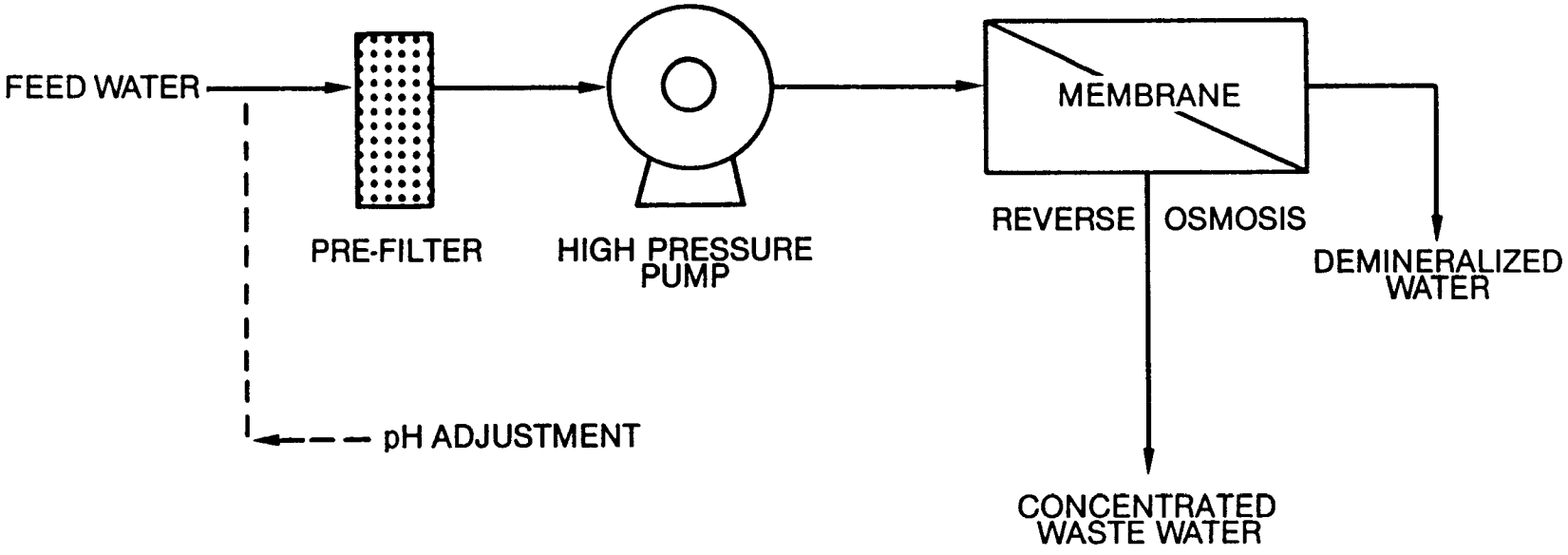


FIGURE 25: CROSS-SECTION OF ELECTRODIALYSIS PROCESS

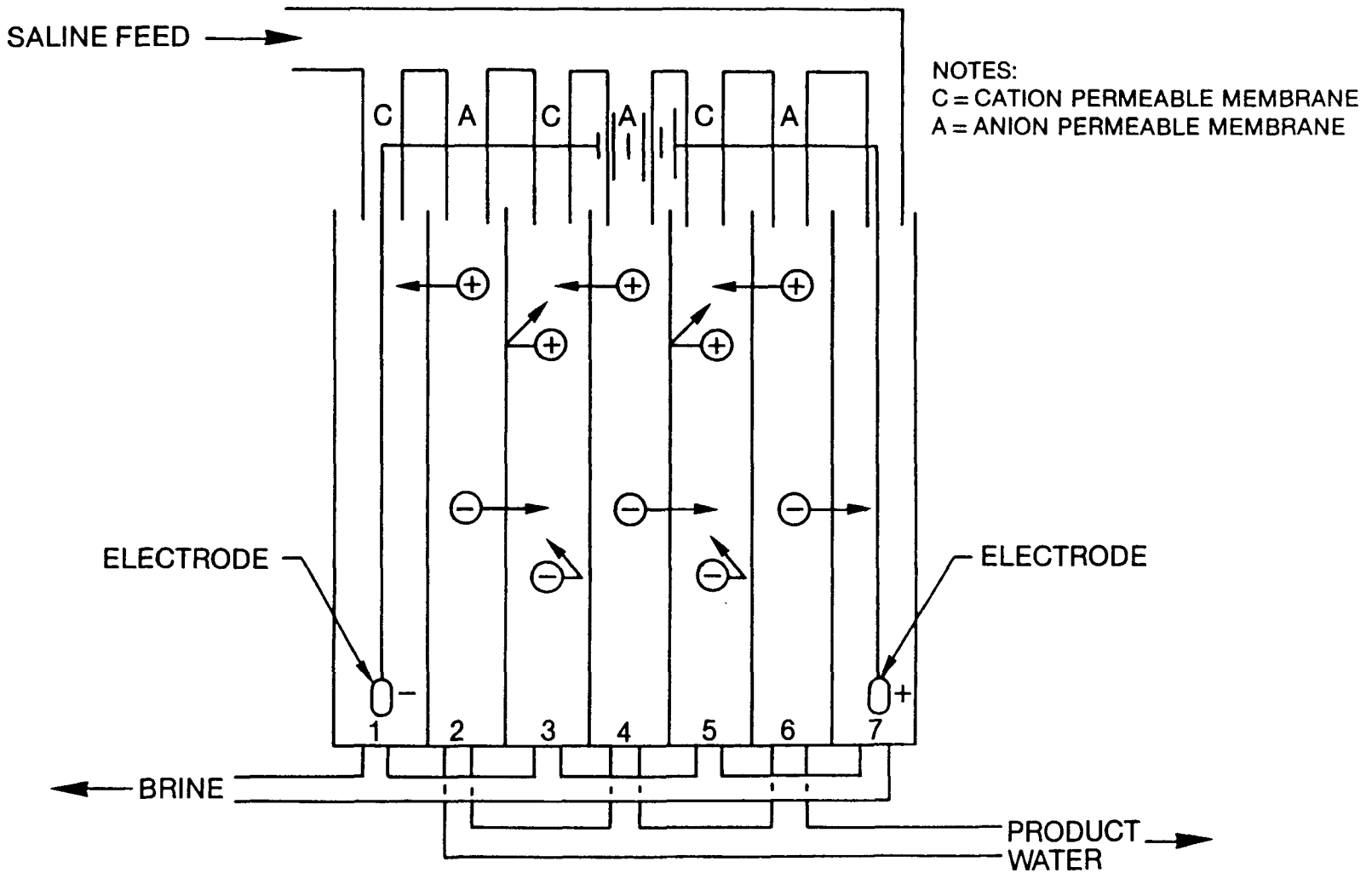


FIGURE 26: SCHEMATIC OF PACKED COLUMN AERATION

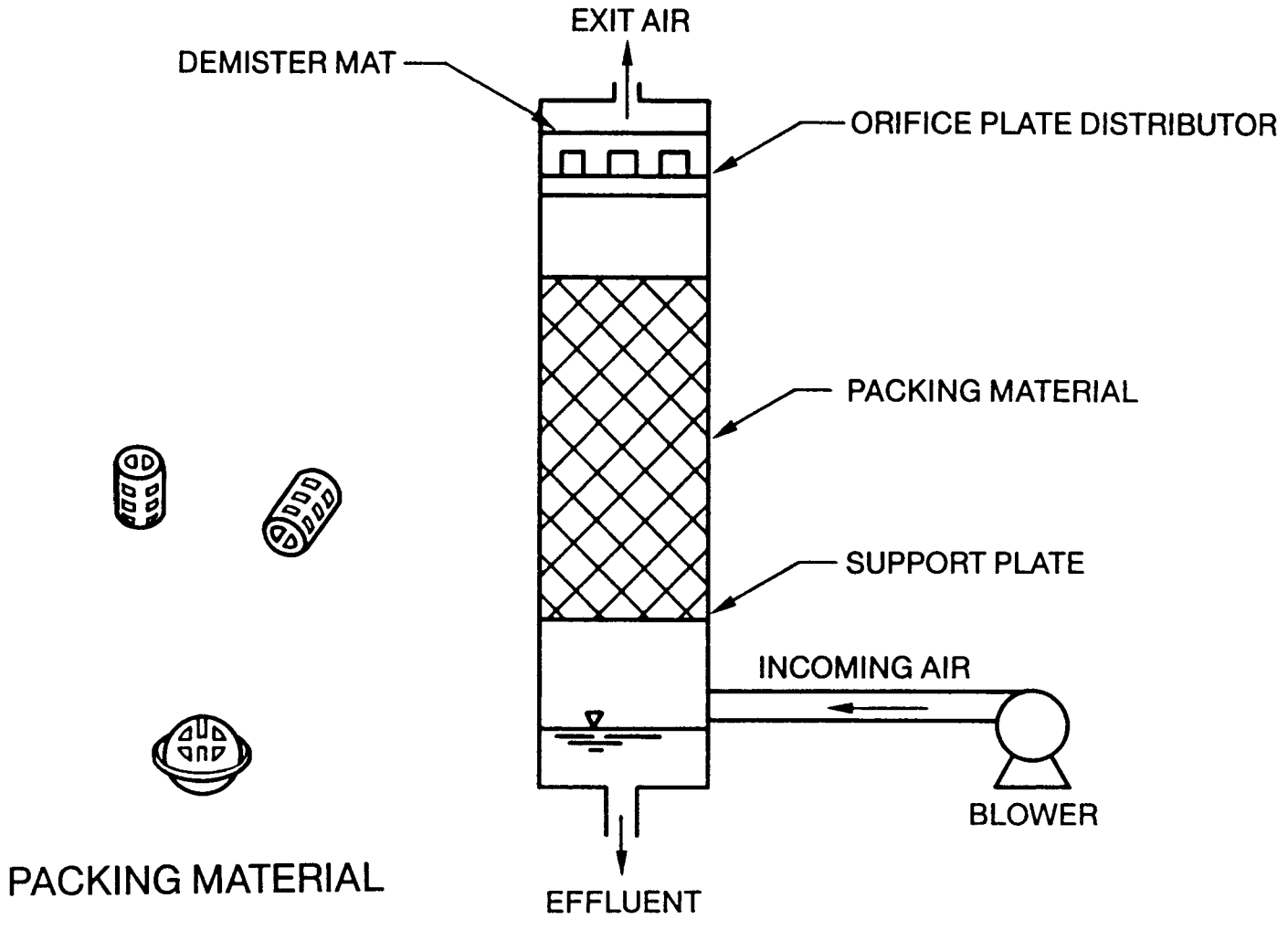
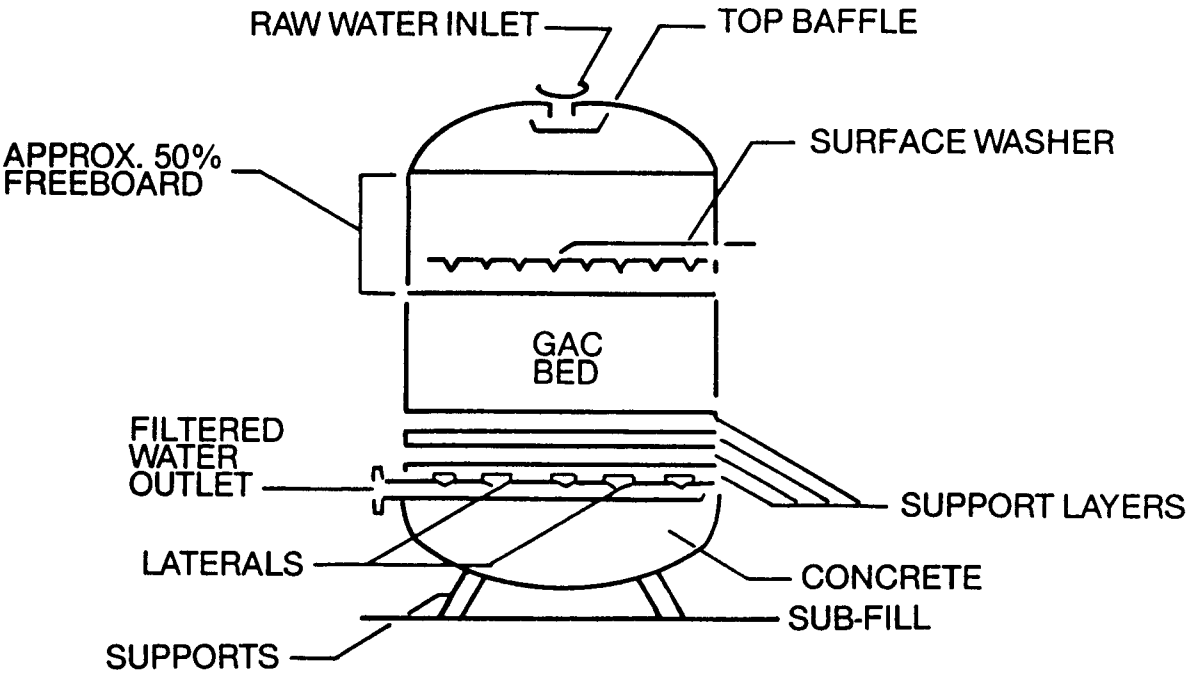
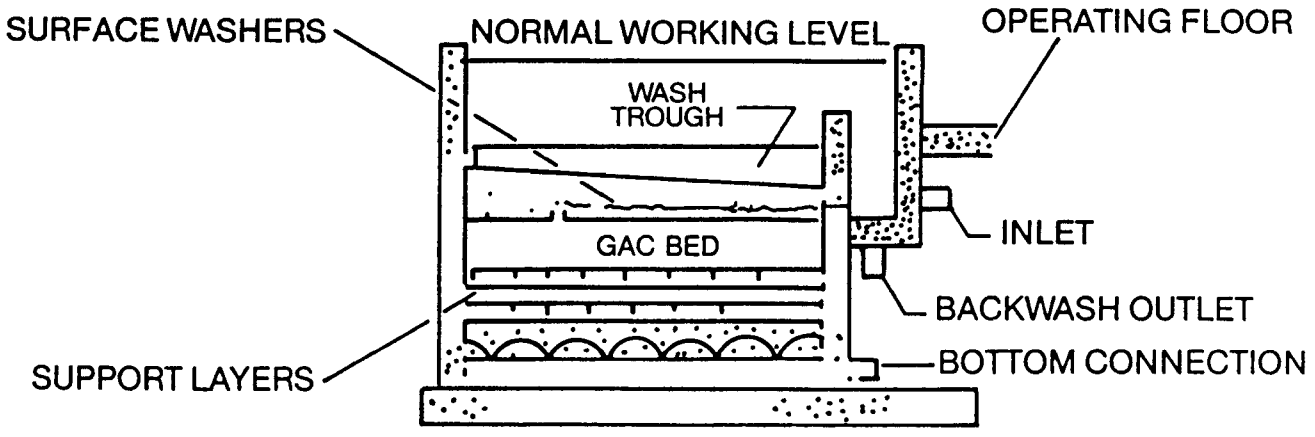


FIGURE 27: SCHEMATICS OF CARBON CONTACTORS



PRESSURE CONTACTOR



GRAVITY CONTACTOR

c) Processes as a function of molecular weight and solubility[6] [Figure 28]

d) Aeration is generally more cost-effective[15]

D. Decentralized treatment

1. Most technologies are available in sizes to treat single buildings (point-or-entry) and single taps (point-of-use)[11] [Figure 29]

2. Point-of-use is only acceptable for short term emergency use since it only treats one tap

3. Point-of-entry devices treat all the water in a single building -- maintenance by service contract.

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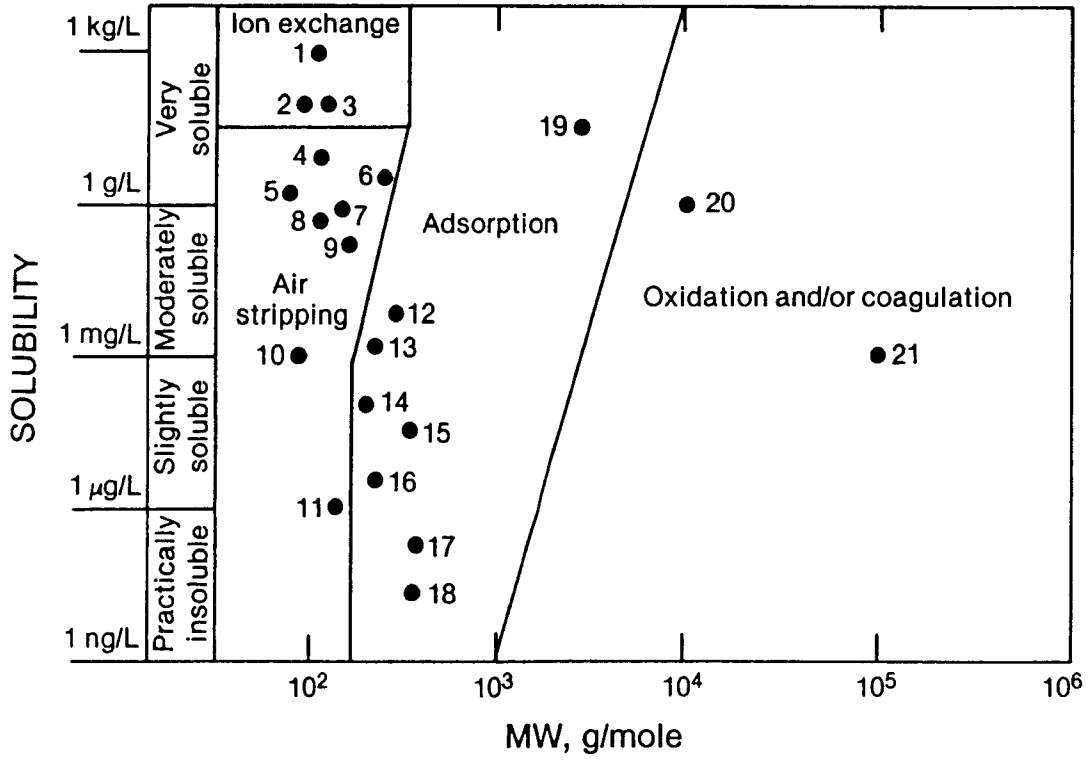
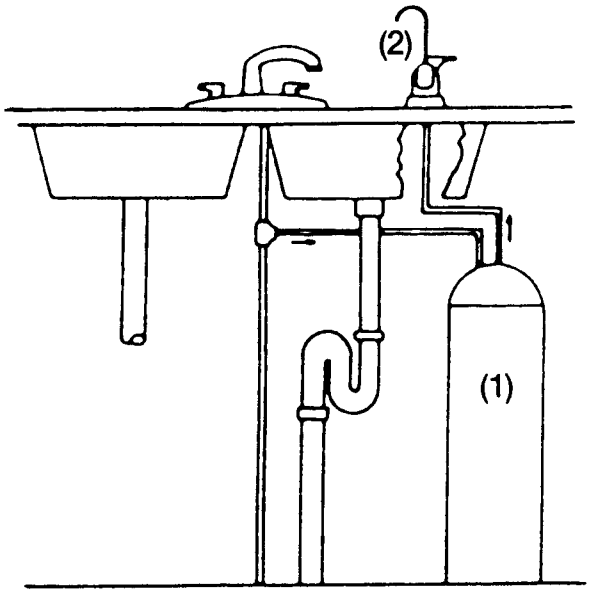
FIGURE 28: TREATMENT PROCESSES FOR ORGANICS REMOVAL



KEY TO NUMBERED COMPOUNDS

1 Resorcinol
2 Phenol
3 Hexanoic acid
4 Chloroform
5 Benzene
6 Bromoform
7 Carbon tetrachloride
8 Chlorobenzene
9 Perchloroethylene
10 Hexane
11 Decane
12 Lindane
13 Arochlor 1232 (PCB)
14 Pyrene
15 Arochlor 1254 (PCB)
16 Benzo(a)pyrene
17 Dieldrin
18 Aldrin
19 Amylose
20 Fulvic acid
21 Humic acid

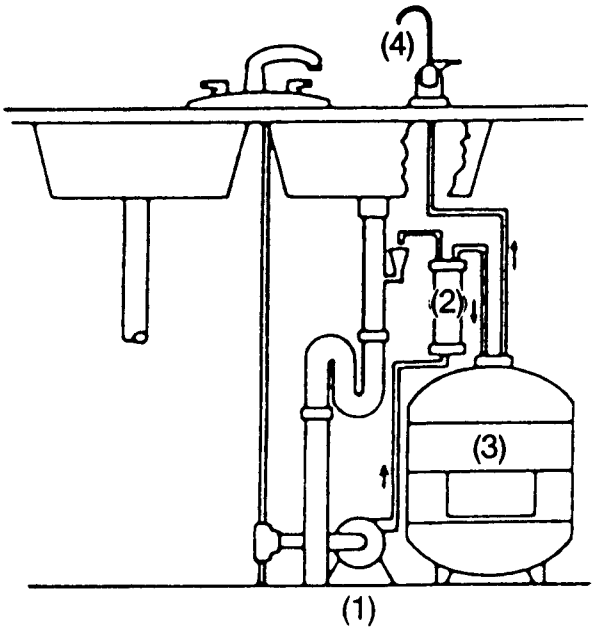
FIGURE 29: POINT-OF-USE-DEVICES



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

8. Westrick, J. J., J. W. Mellow, and R. F. Thomas. 1984 "The Ground Water Supply Survey". Journal American Water Works Association. Vol. 76. No. 5. p. 52.

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14. Dobbs, R. A. and J. M. Cohen. 1985. "Isotherms for Toxic Organics". EPA 600/880-023. Office of Research and Development, Wastewater Treatment Division. Cincinnati, Ohio.

15. AWWA Research Foundation. "Occurrence and Removal of Volatile Organic Chemicals from Drinking Water", Cooperative Research Report with KIWA. AWWA Research Foundation. Denver, Colorado.

Part IIIB

Inorganics Treatment
Overview and Case Studies

Part IIIB

WORKSHOP ON

RISK ASSESSMENT AND MANAGEMENT

OF

DRINKING WATER CONTAMINATION

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.

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.

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. This 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

   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.

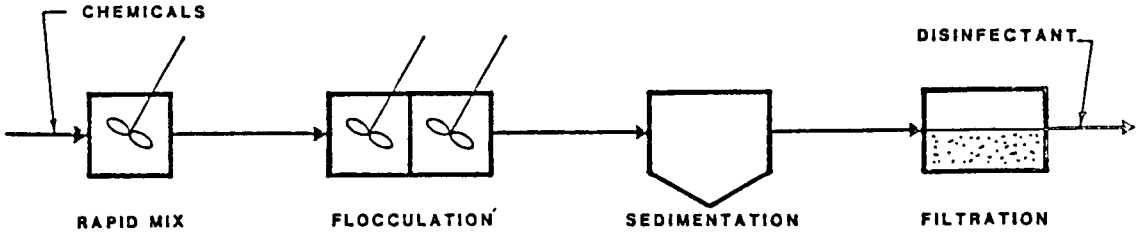


FIGURE - SCHEMATIC OF
COAGULATION/FILTRATION PROCESSES

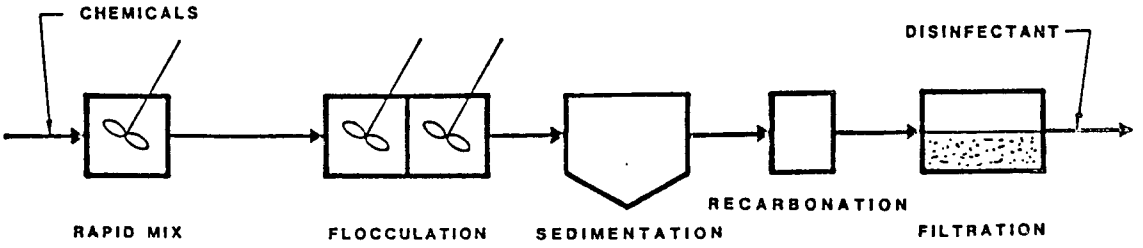


FIGURE - SCHEMATIC OF
LIME SOFTENING PROCESSES

B. 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 following 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

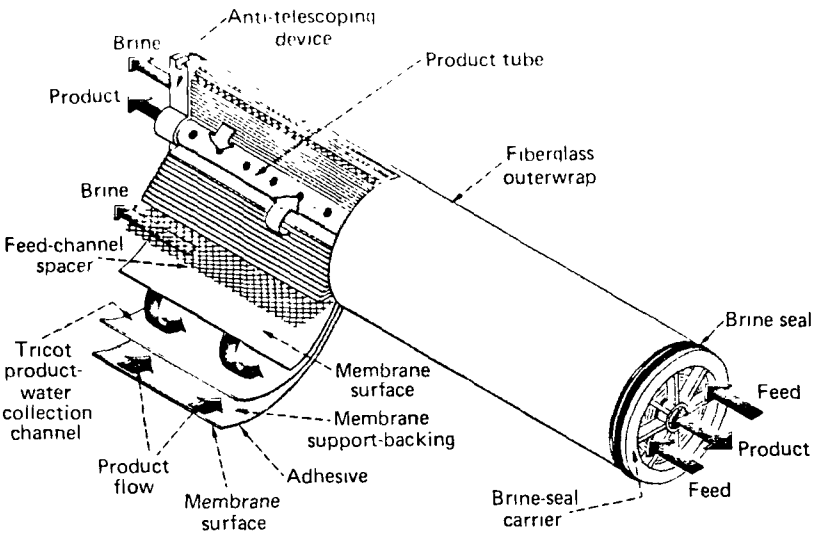
5. Limitations - in general the process is effective in removing cations and fluoride. The process does not effectively remove Cr (IV), nitrate, selenium or mercury.

C. Reverse Osmosis

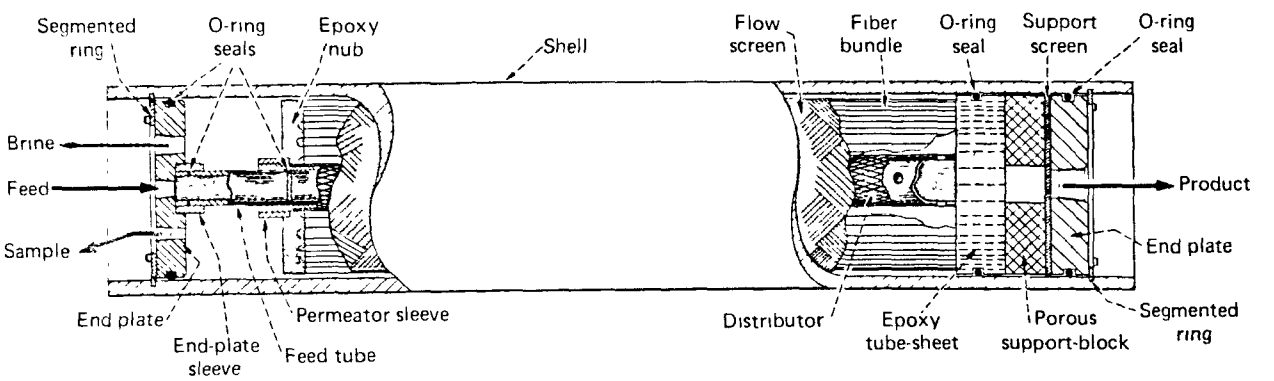
1. Process used for the desalting of sea water or brackish groundwaters. Inorganic chemicals are removed by retention in the brine by the membrane. Several types of membranes are available including spiral wound and hollow fiber with some membranes designated as high pressure (greater than 350 psi) or low pressure (below 250 psi). Examples of spiral wound and hollow fiber membranes are presented on Figure I-1. A process schematic is presented as Figure I-2.

2. Typical unit processes include:
   - raw water pumpage
   - pretreatment
   - membrane desalination
   - disinfection
   - storage and distribution

TYPES OF REVERSE OSMOSIS MEMBRANES



SPIRAL WOUND



HOLLOW FIBER

REVERSE OSMOSIS

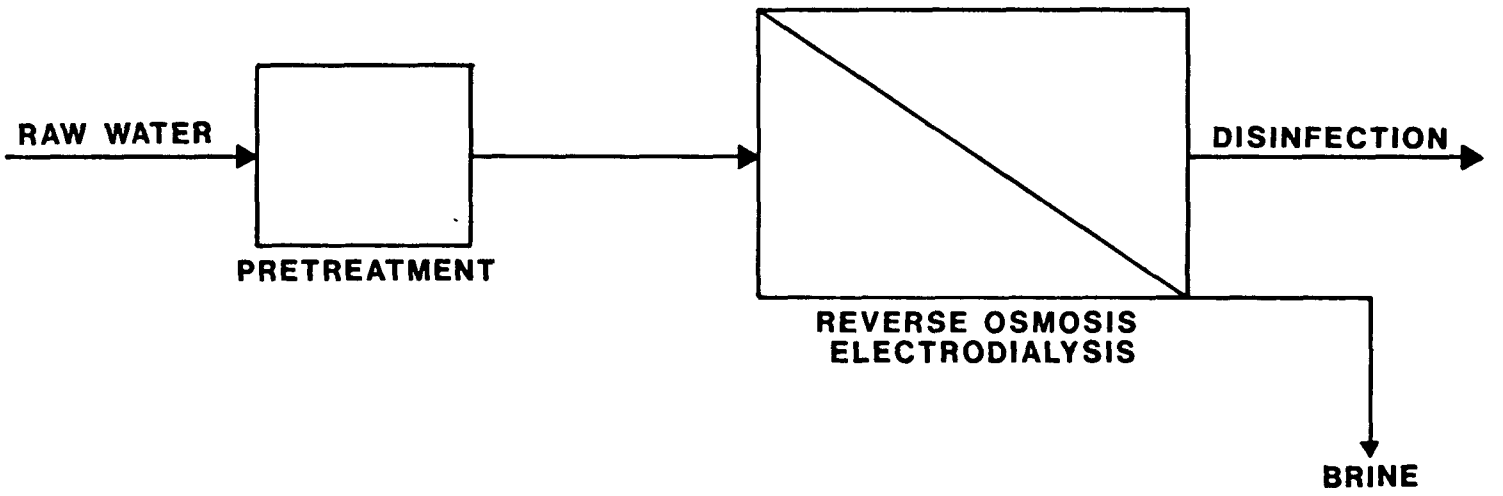


FIGURE I-2

3. Process design considerations
   - influent suspend 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.

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

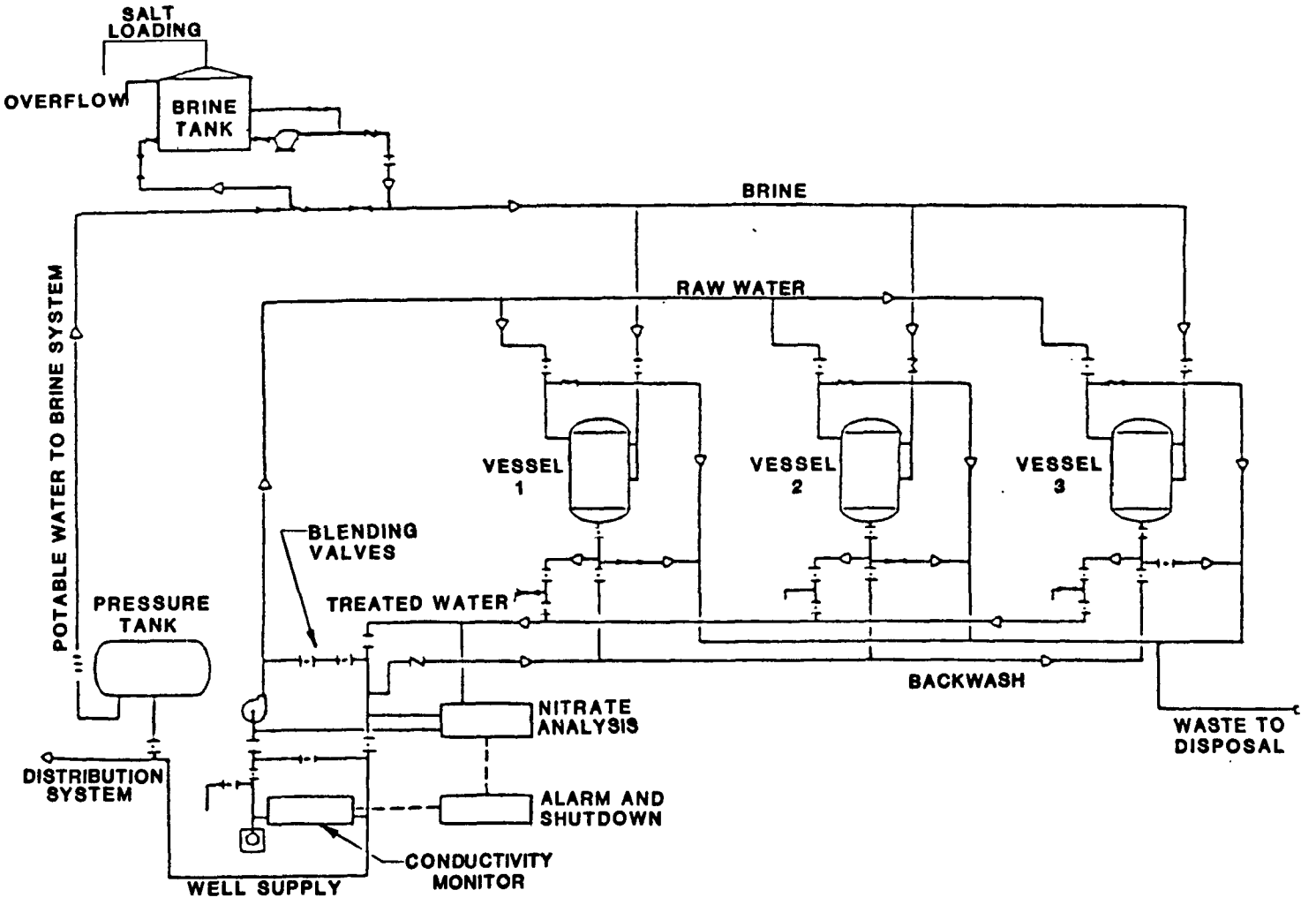
b. Water Quality (Raw)
1) Nitrate: 6.8 to 22.1 mg/L as N

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



IIIB-10

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

- 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

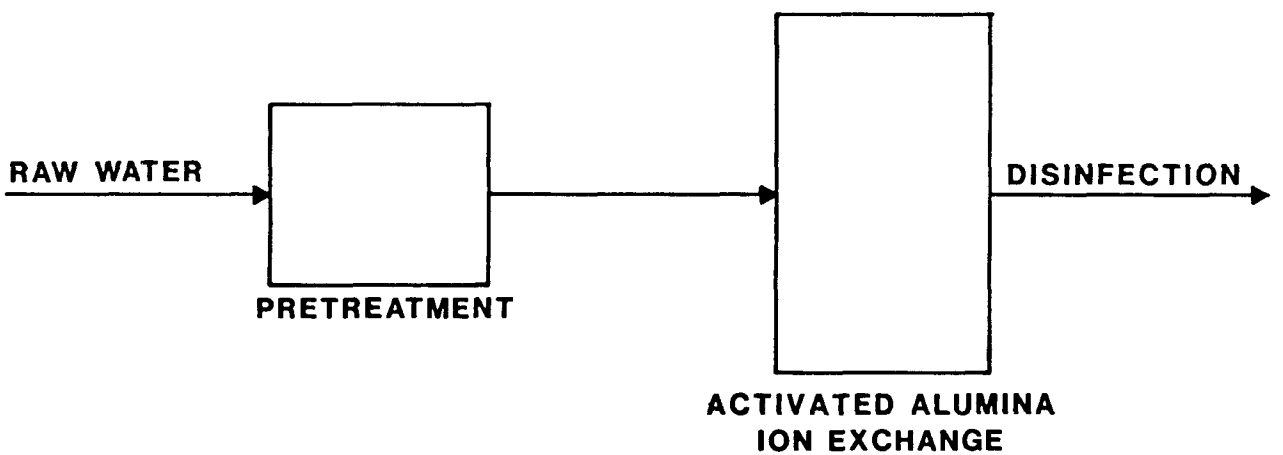


FIGURE III-1

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)

BASIC OPERATING MODE FLOW SCHEMATICS

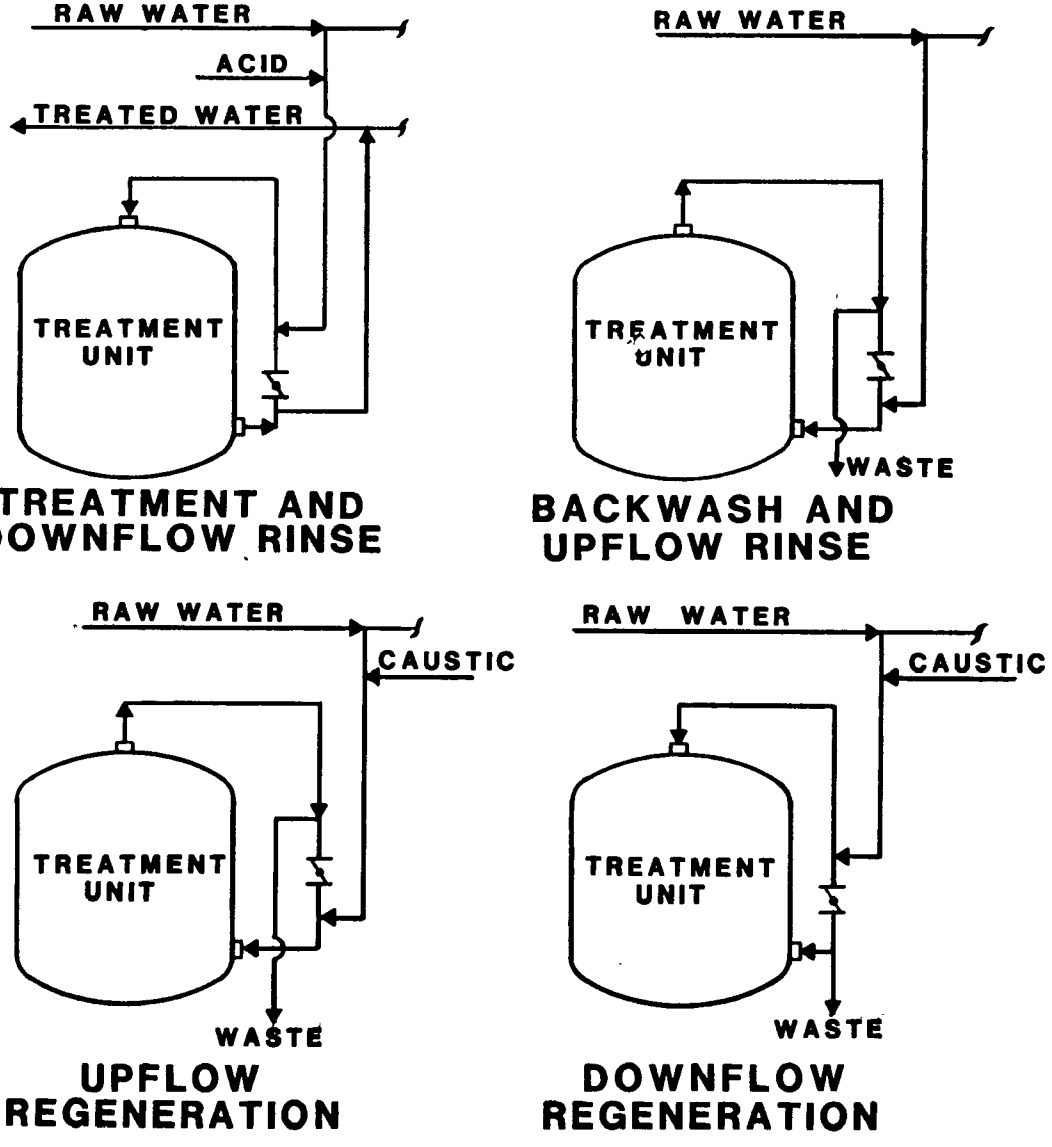


FIGURE III-

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.

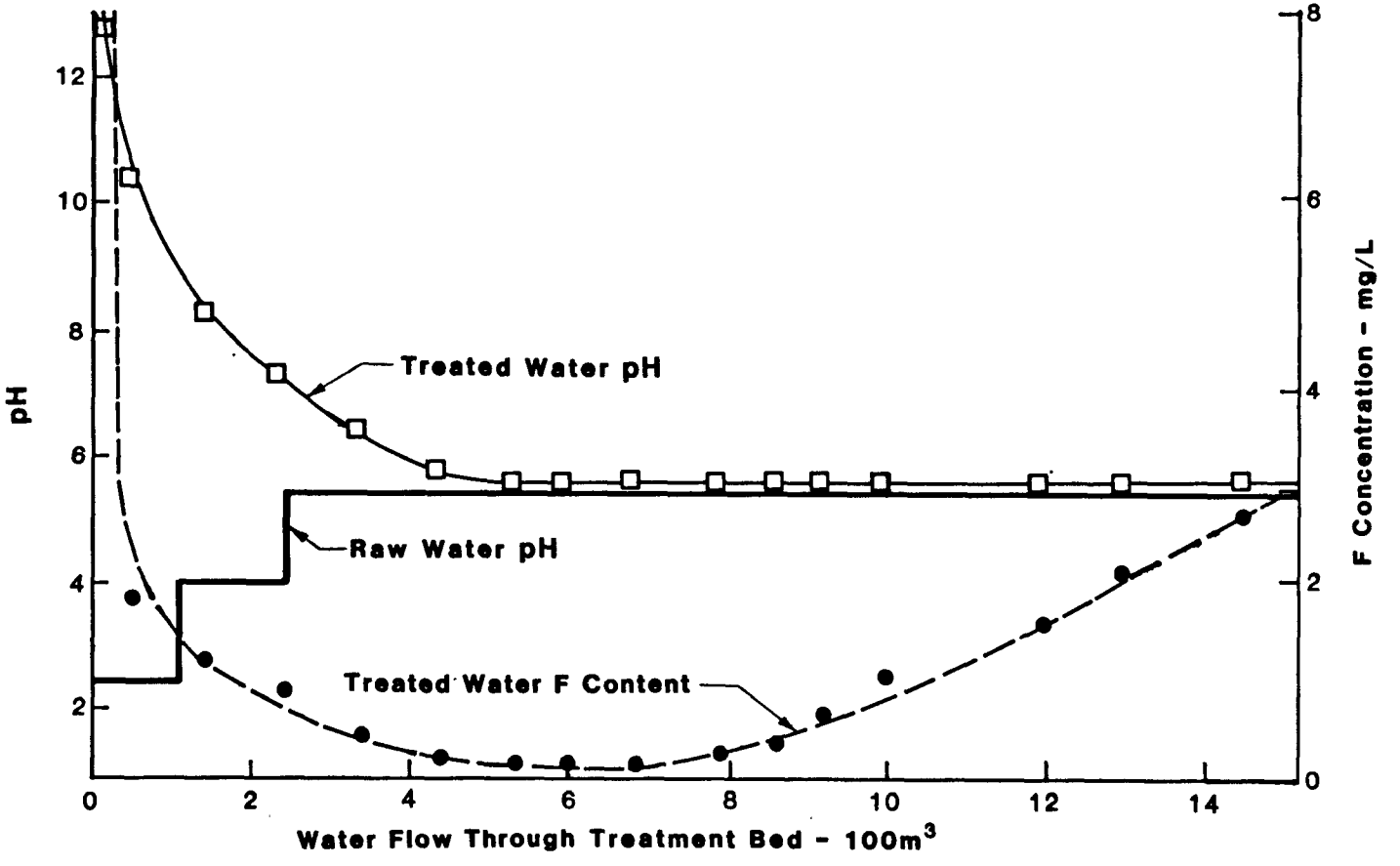


FIGURE III-3

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 producesludges
    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

7. The most probable application for each treatment process is summarized in Table IV-1.

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

Part III C

ORGANICS TREATMENT

OVERVIEW AND CASE STUDIES

WORKSHOP ON

RISK ASSESSMENT AND MANAGEMENT

OF

DRINKING WATER CONTAMINATION

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

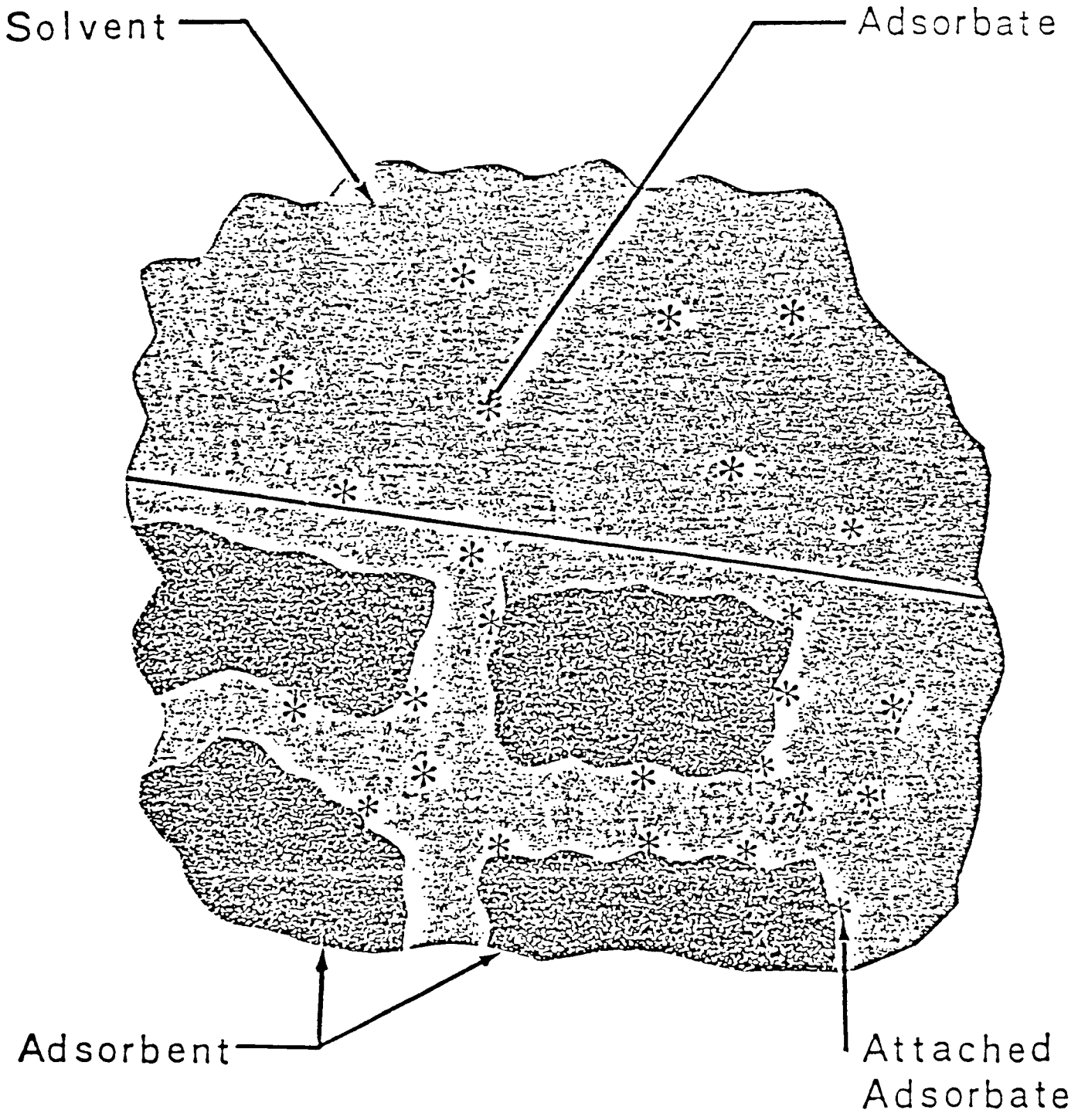
      - high degree of porosity
      - extensive internal surface area
      - affinity of adsorbate for absorbent(polar, nonpolar)

   c. Aqueous Solution

      - temperature
      - pH
      - dissolved solids
      - other adsorbates

4. Forms of Activated Carbon

   a. Granular
   b. Powdered



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

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

lb/MG

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

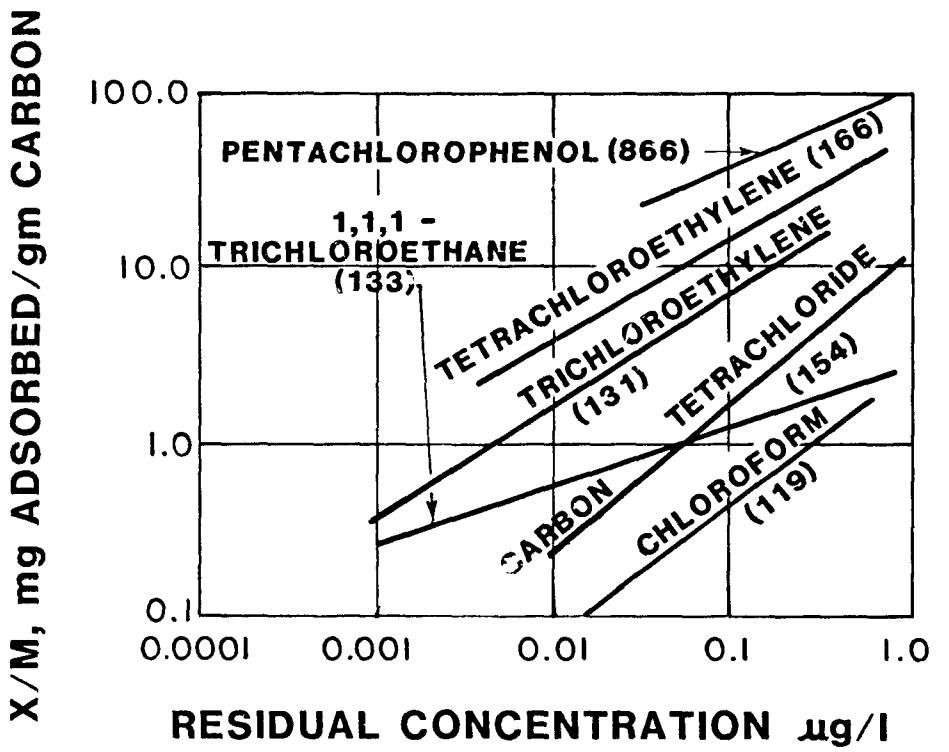
2. Carbon Contactor Configuration

a. Upflow

- long contact times
- suspended solids removal

b. Downflow

- Pressure - see diagram on Figure I-6
- Gravity - see diagram on Figure I-7



NOTE: NUMBER IN PARENTHESIS (166) INDICATES THE MOLECULAR WEIGHT OF THE COMPOUND

ADSORPTION ISOTHERMS FOR SEVERAL ORGANIC COMPOUNDS FOUND IN GROUND WATER SUPPLIES

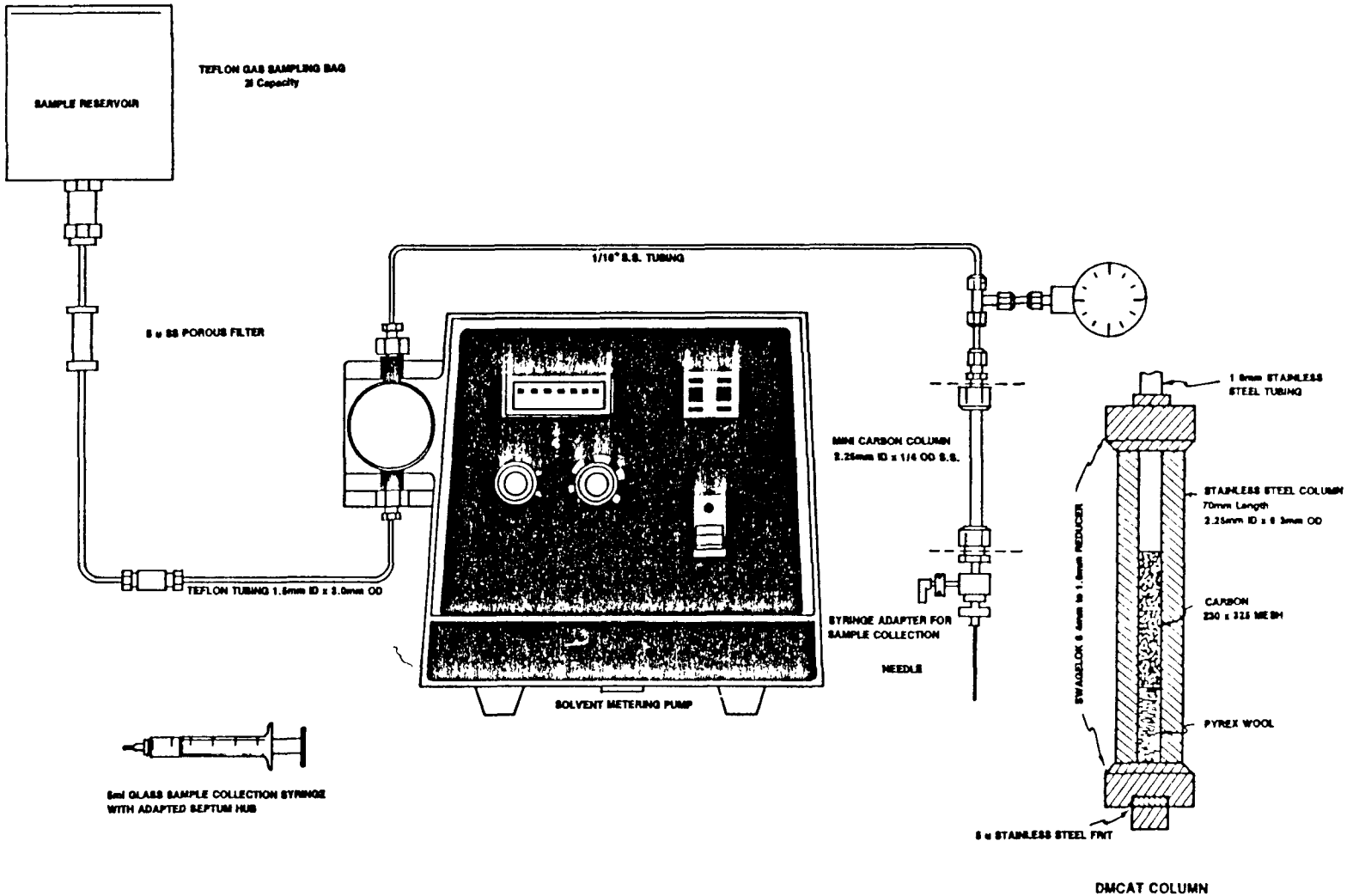
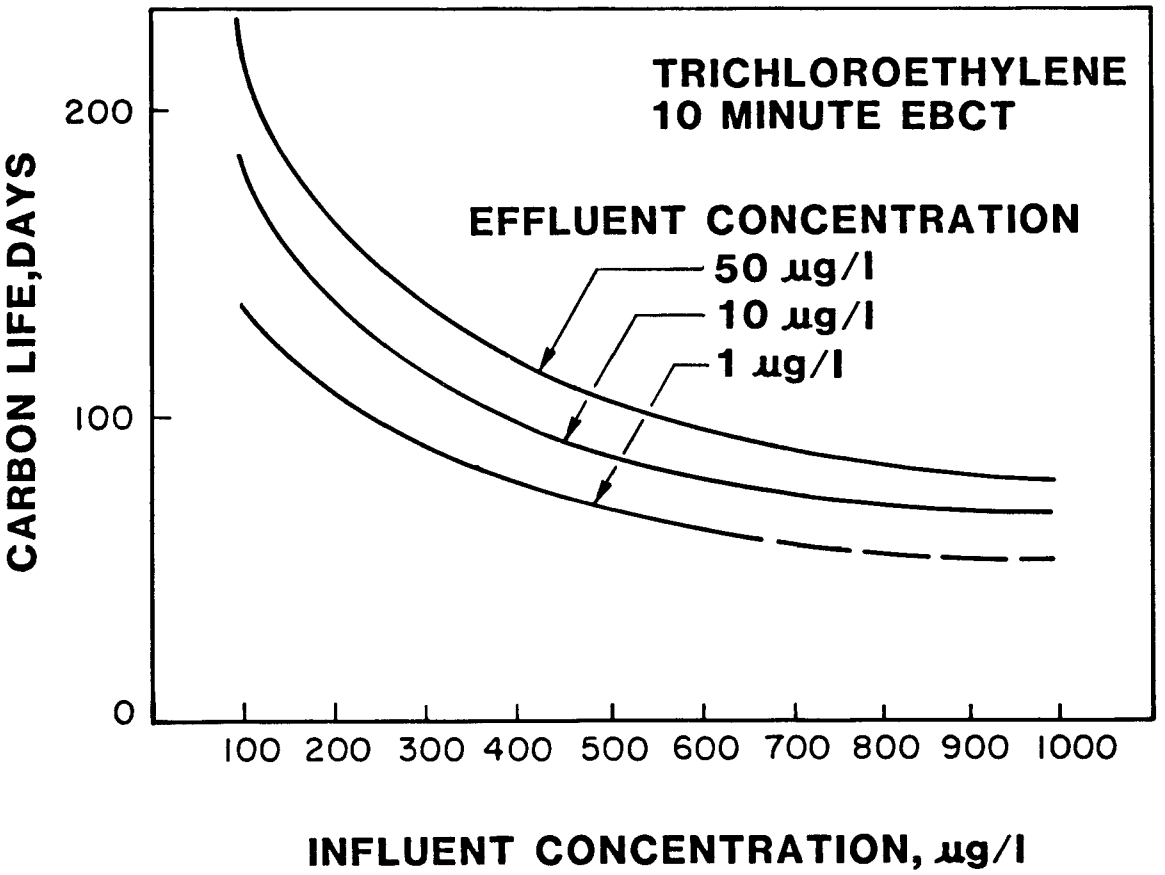
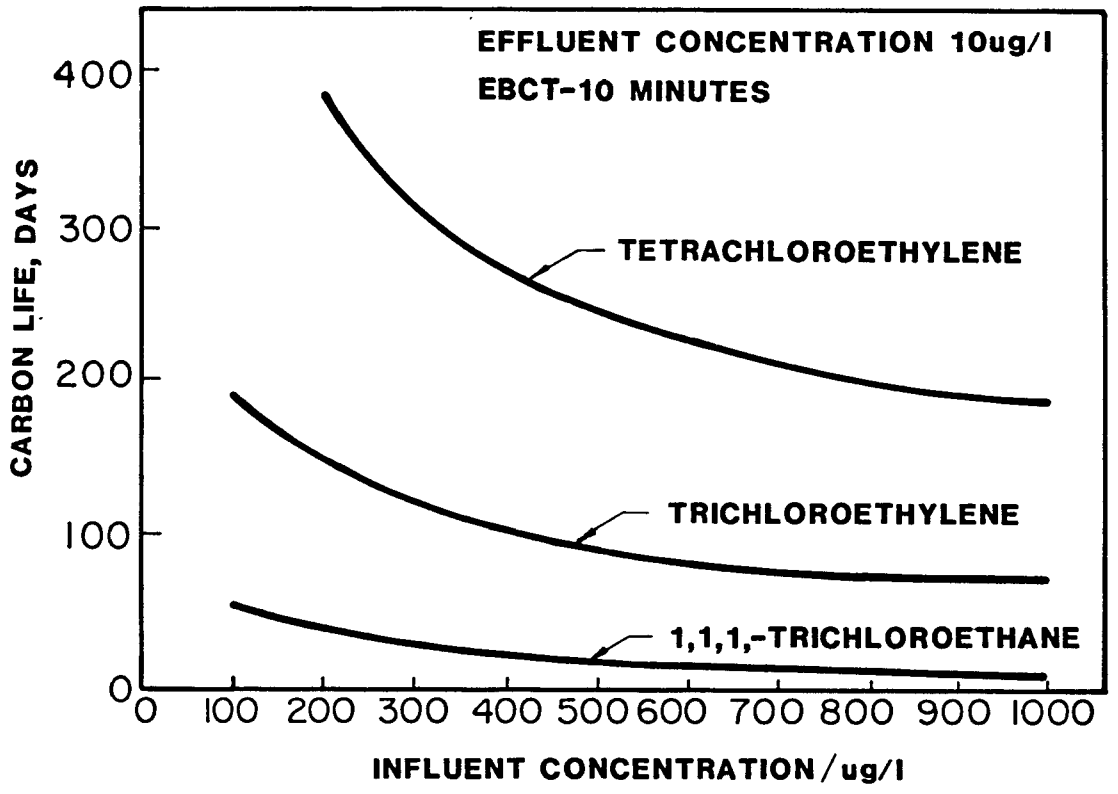


DIAGRAM OF DYNAMIC MINI-COLUMN ADSORPTION TECHNIQUE SYSTEM

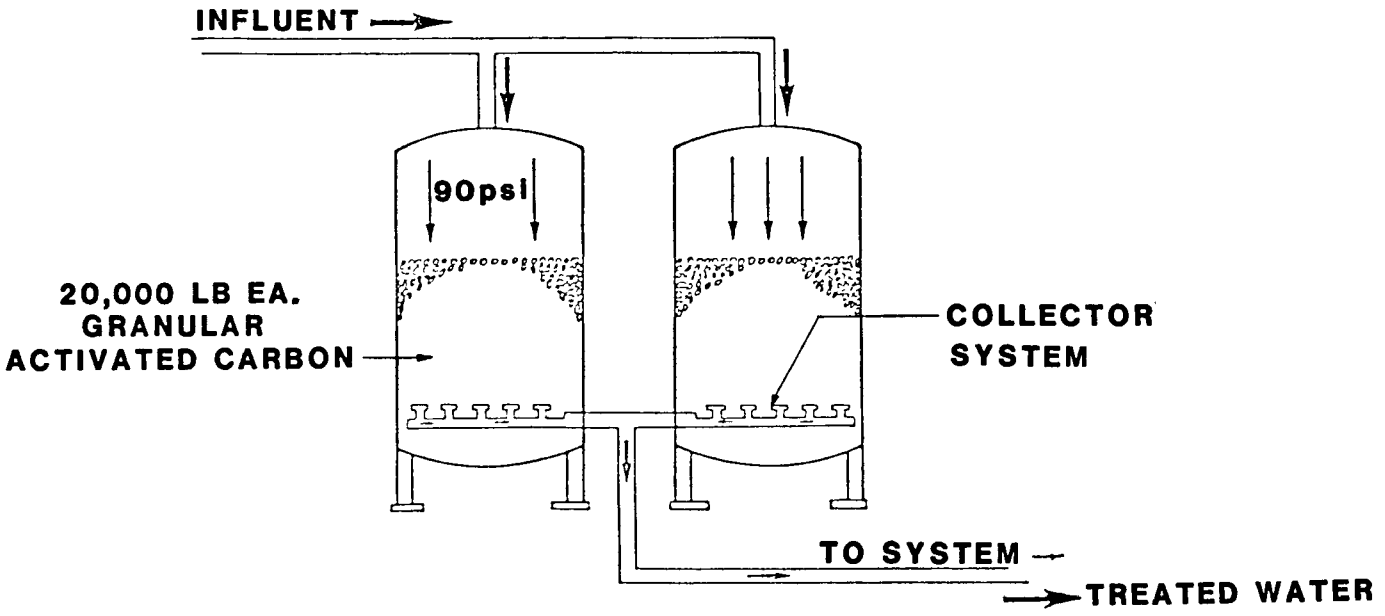
FIGURE I-3



EFFECT OF CONTAMINANT LEVELS ON CARBON LIFE

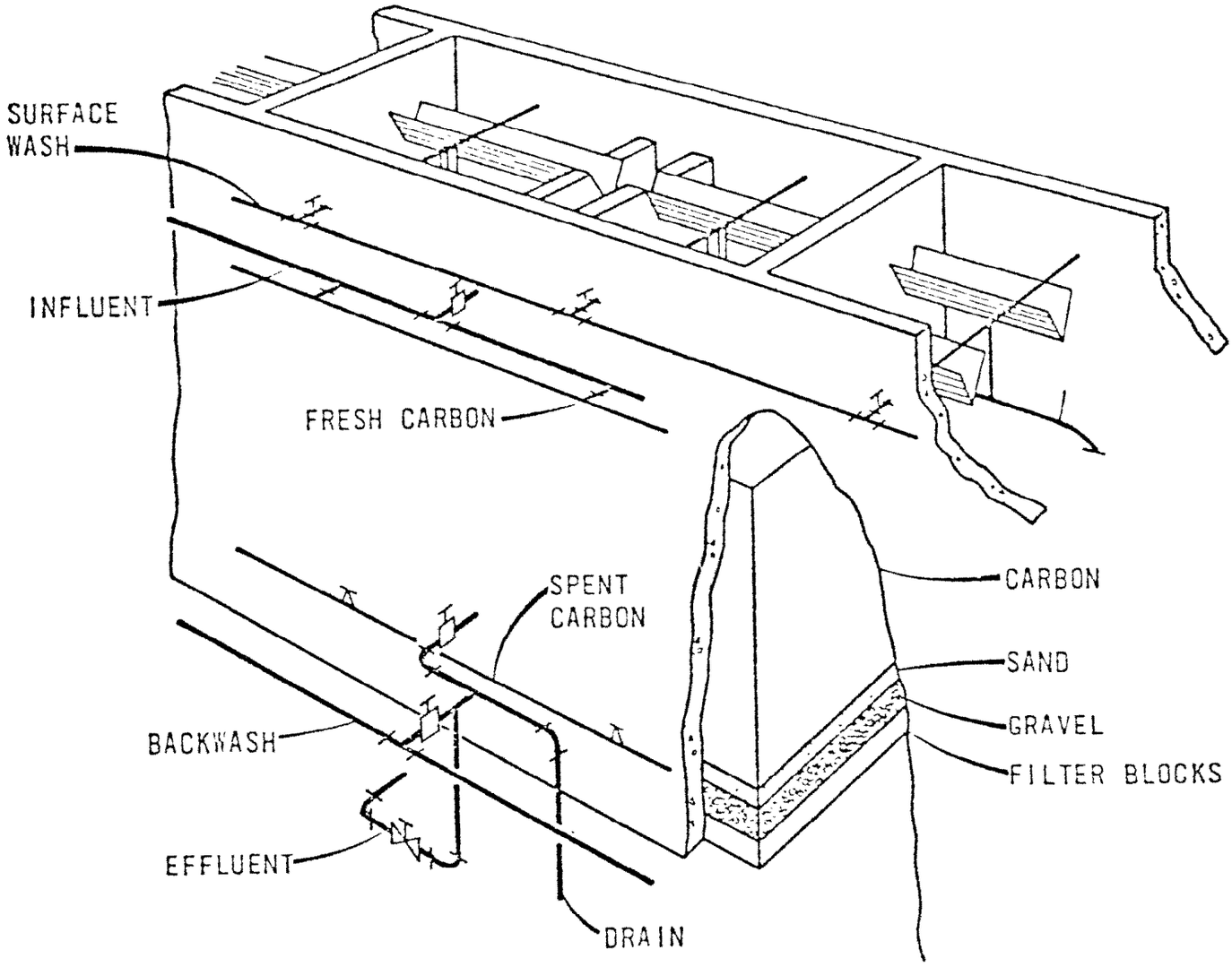


EFFECT OF TYPE OF COMPOUND ON CARBON LIFE



GAC CONTACTORS

SCHEMATIC OF TREATMENT PROCESSES



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

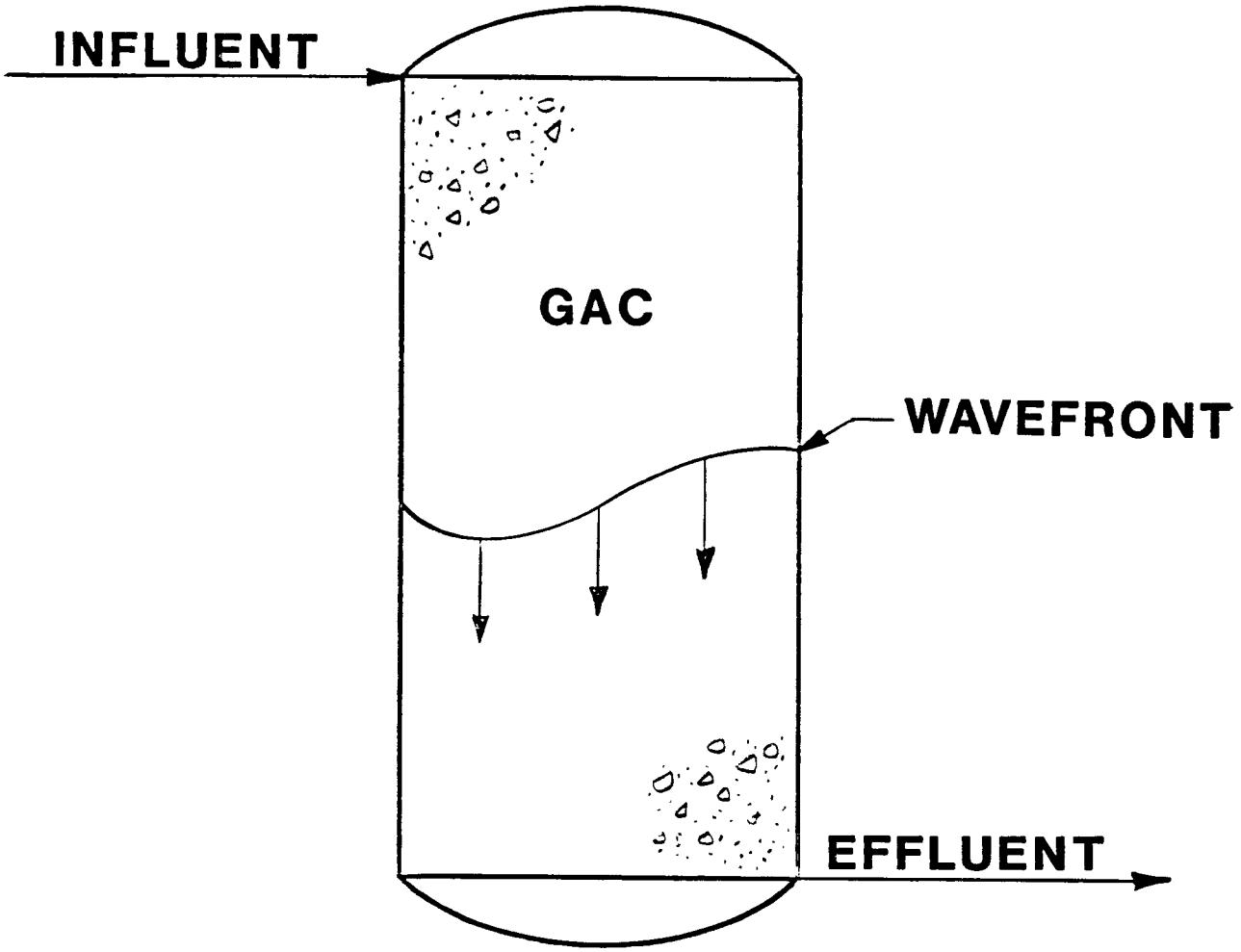
   a. Backwash
   b. Spent carbon

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.



GAC CONTACTOR

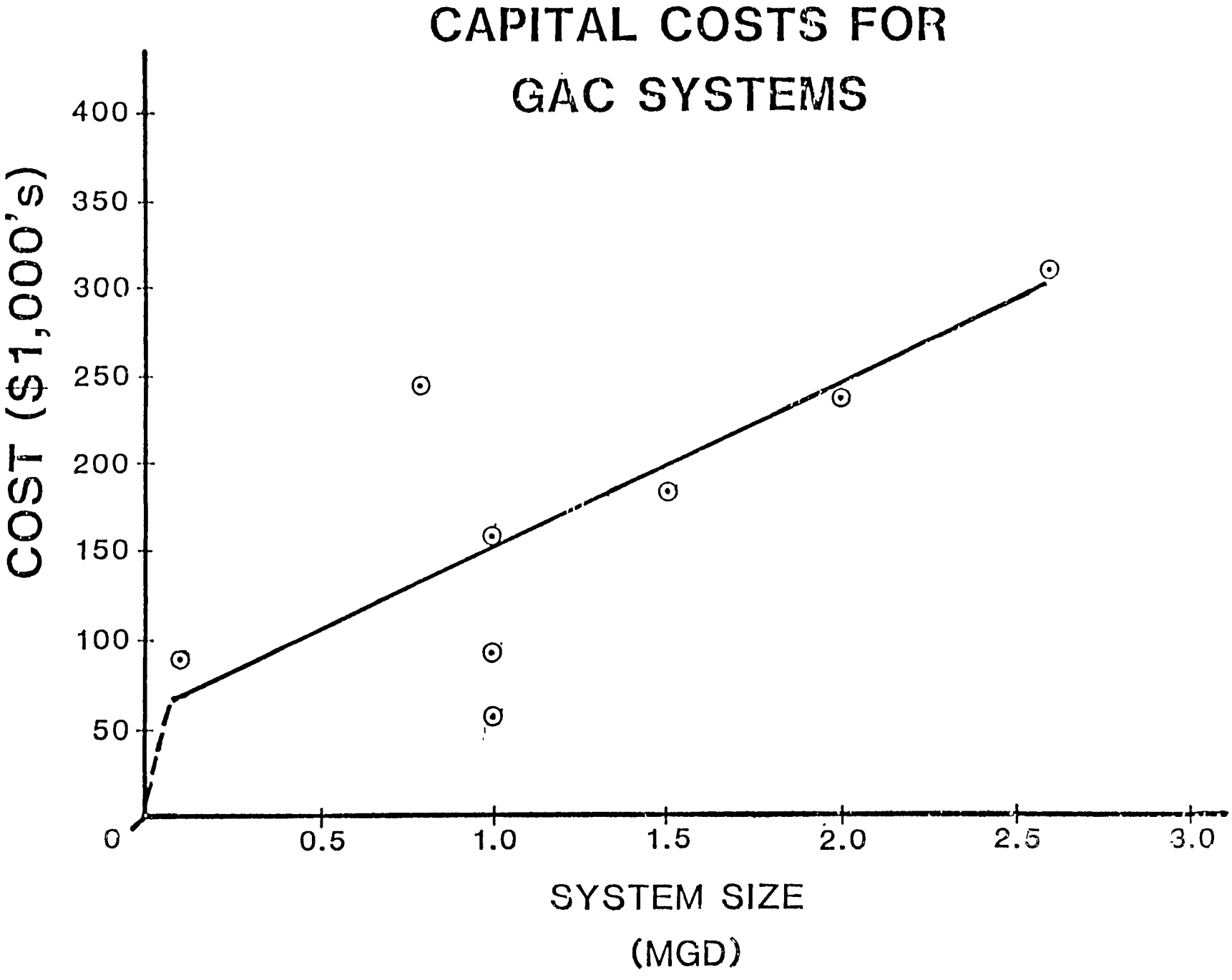

CAPITAL COSTS FOR
GAC SYSTEMS
COST ($1,000's)
400
350
300
250
200
150
100
50
0
0.5
1.0
1.5
2.0
2.5
3.0
SYSTEM SIZE
(MGD)

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 -	↓
VOCs -	most costly

O & M COSTS FOR GAC SYSTEM

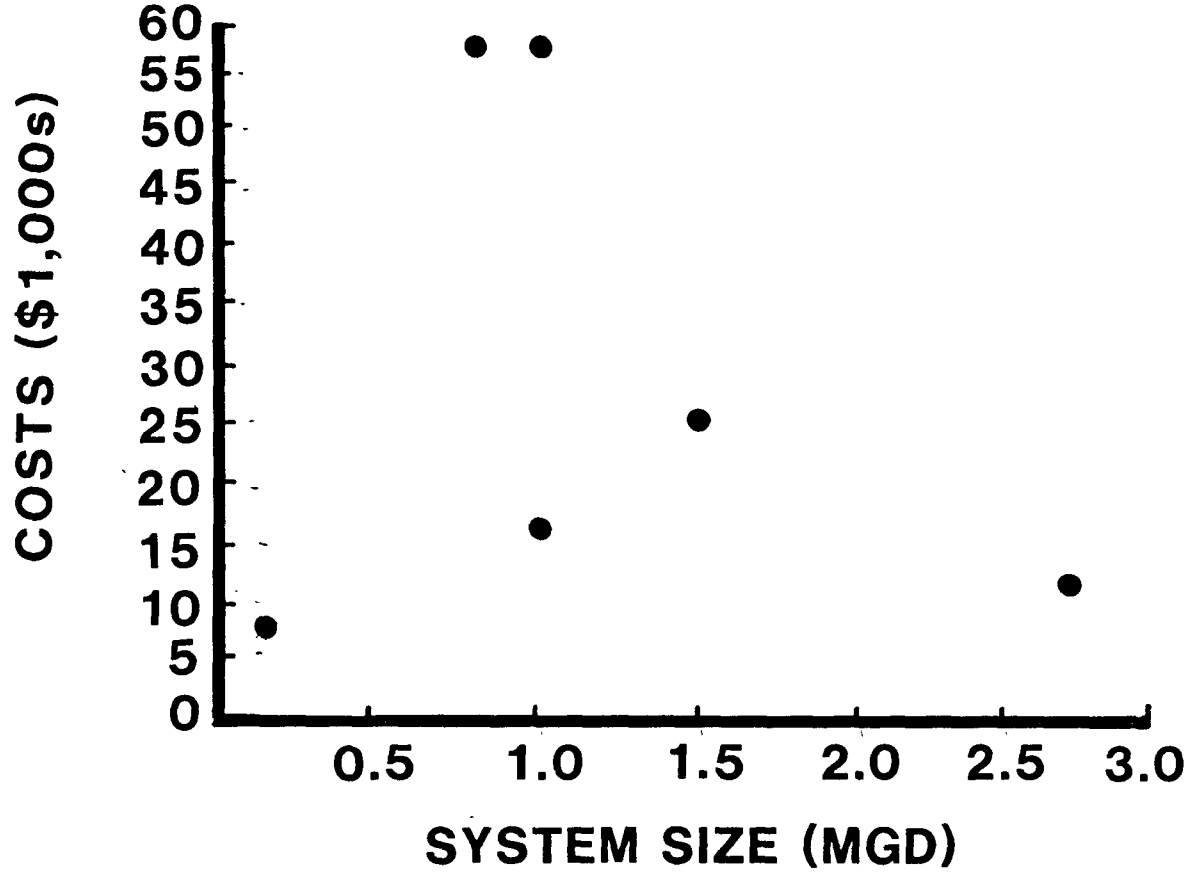


FIGURE I-10

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

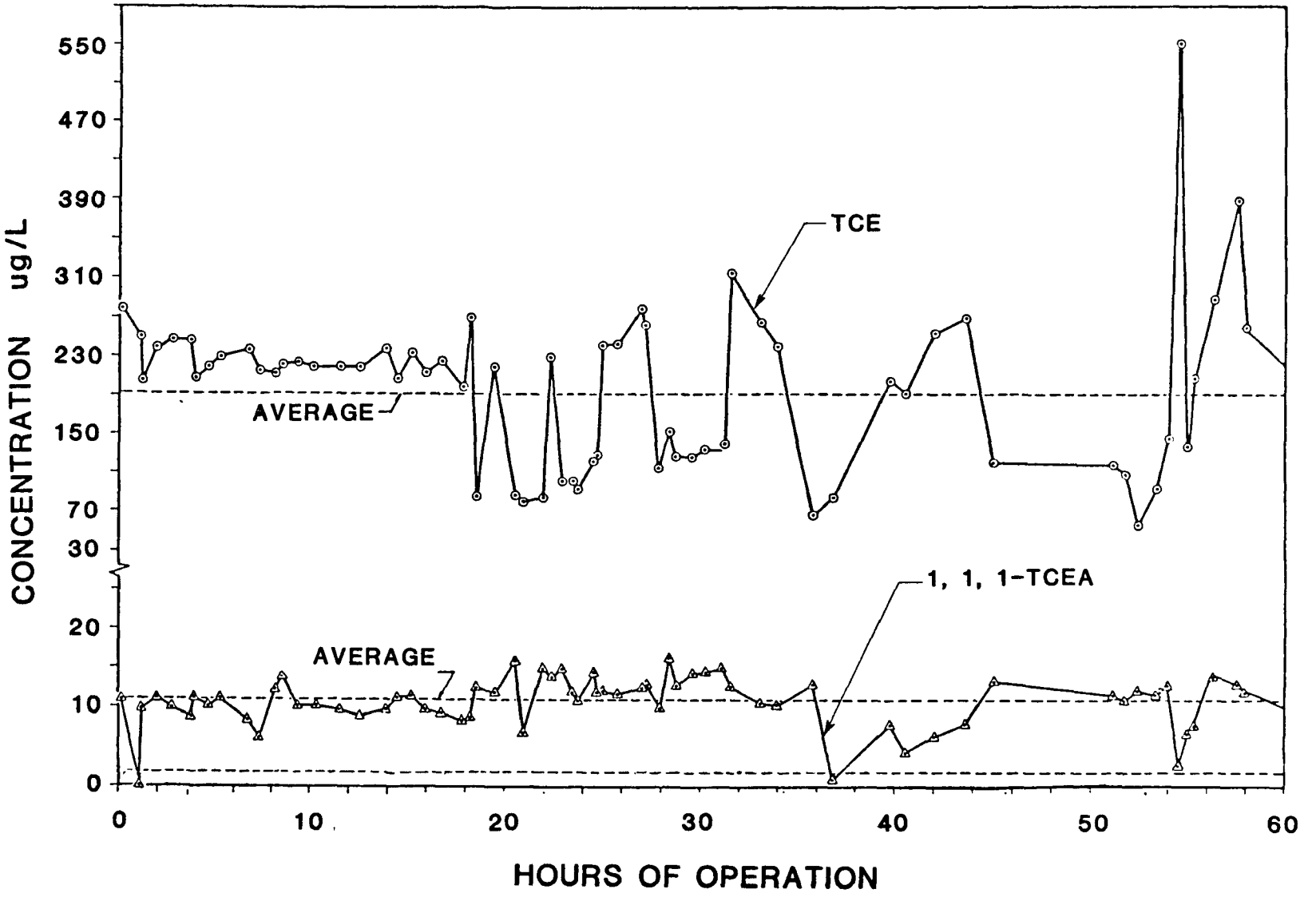


FIGURE II-1

GAC TREATMENT PLANT SCHEMATIC
VANNATTA STREET STATION

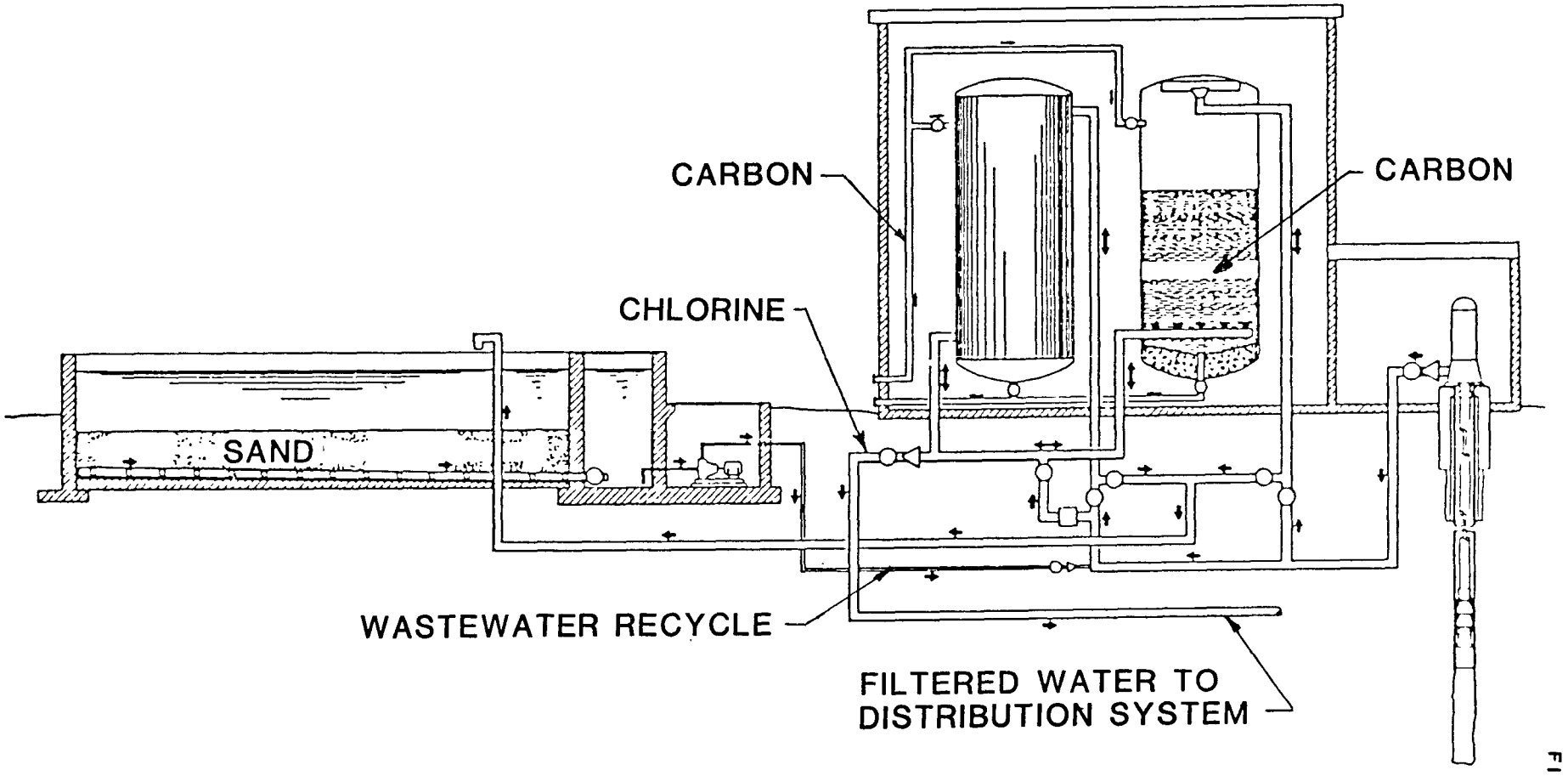


FIGURE II-2

5. Carbon Usage Rates

	lbs GAC/mg
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. GAC ADSORPTION - CINCINNATI, OHIO

1. System Characteristics

a. supply: Ohio River

b. capacity: 220 mgd

c. existing treatment includes: high-rate pretreatment, presettling, conventional treatment (See Figure II-3)

2. Water Quality - see Figure II-4 for influent TOC variations

3. Cincinnati Project Goals

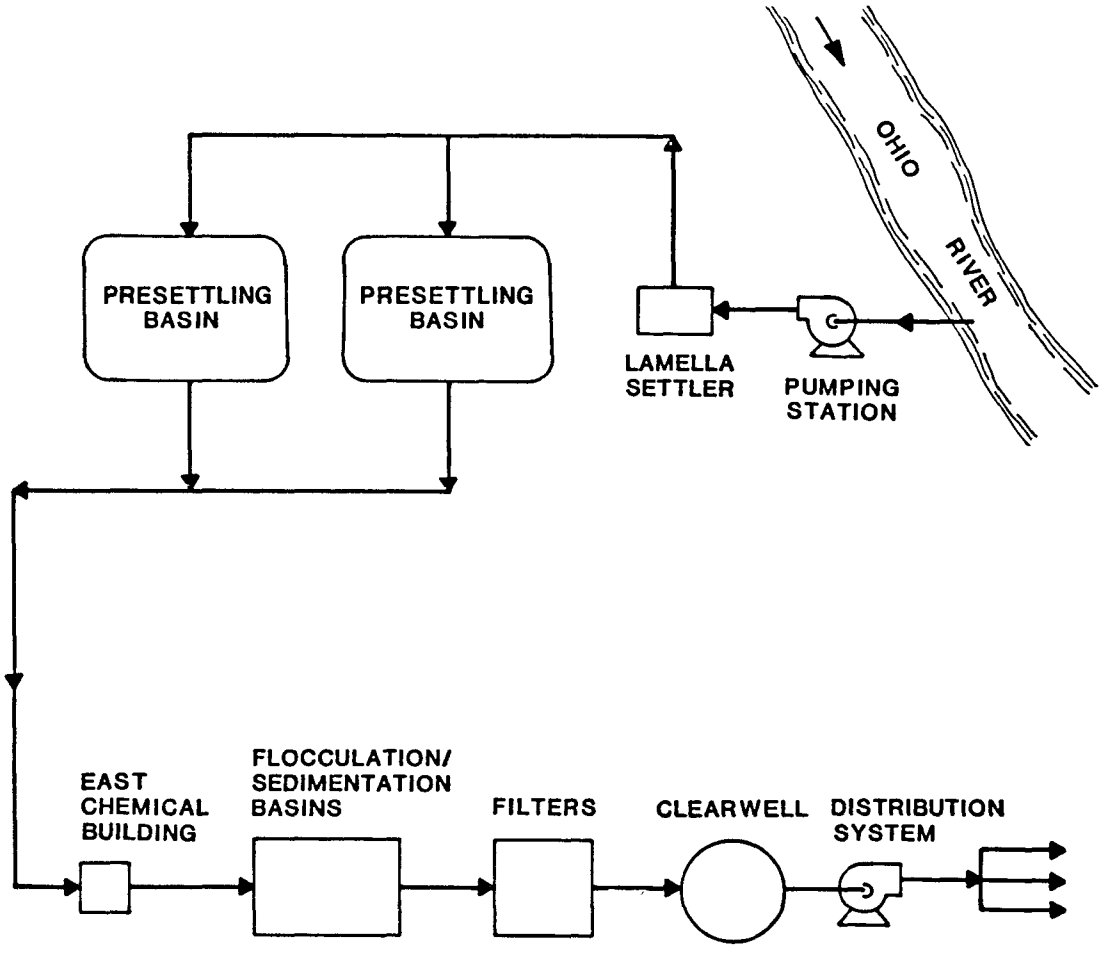
a. Finished water TOC <1.0 mg/L
b. Maximum use of existing WTP facilities
c. Flexible system to accommodate future regulations
d. System costs within reasonable limits

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

CINCINNATI TREATMENT TRAIN



TYPICAL TOC REDUCTION CURVE DURING PILOT STUDY

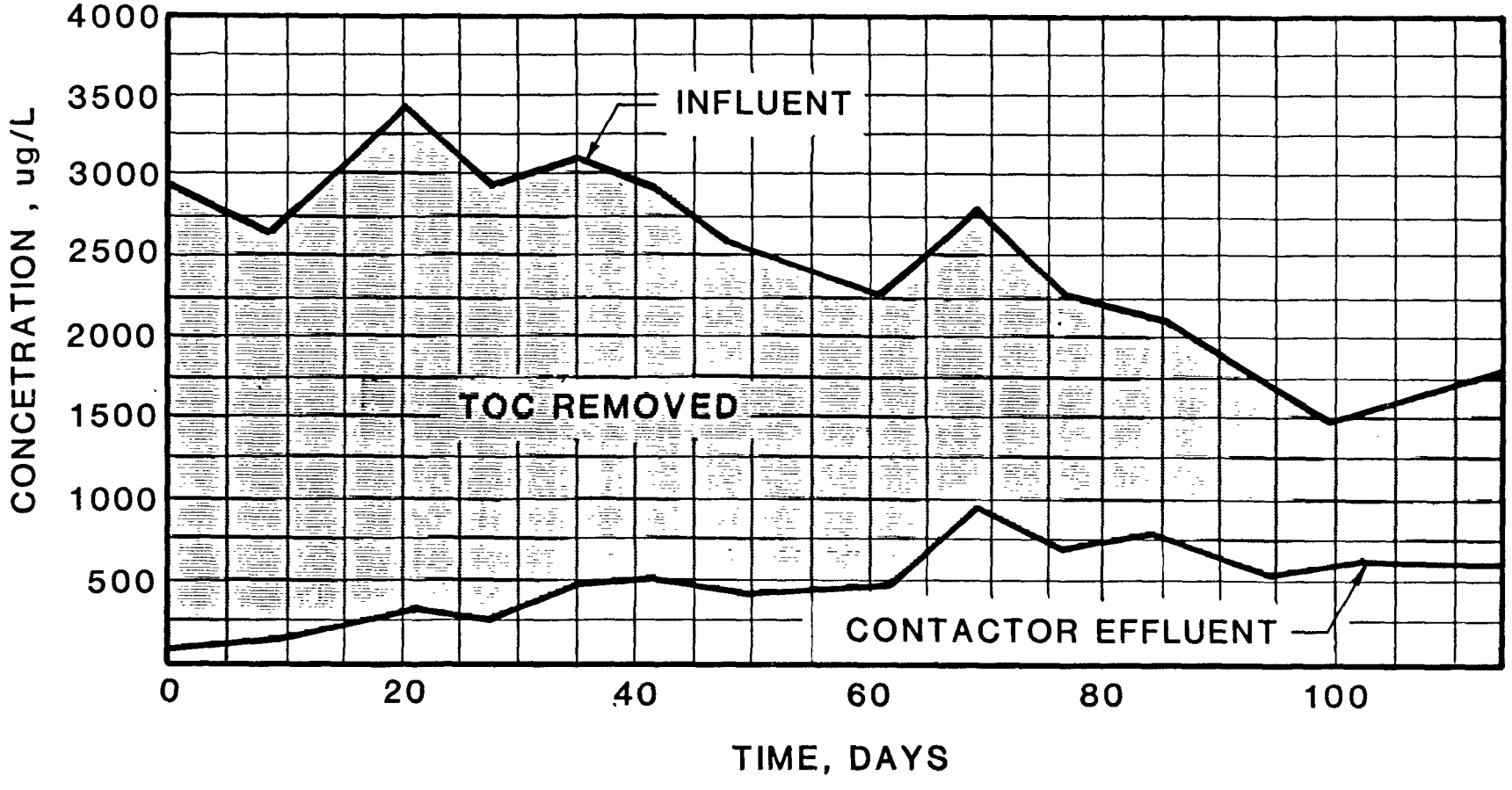
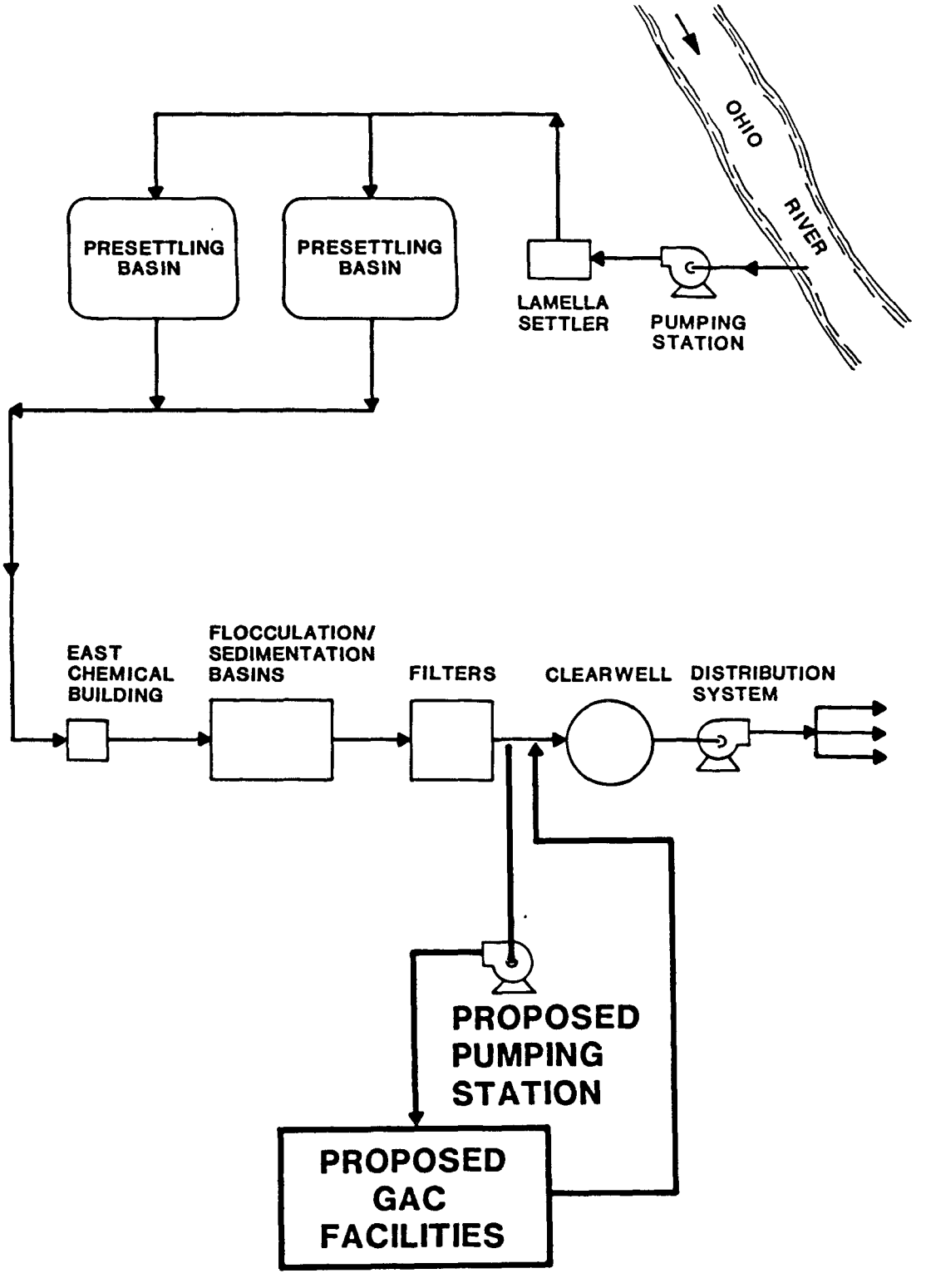


FIGURE II-4

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. blends

        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

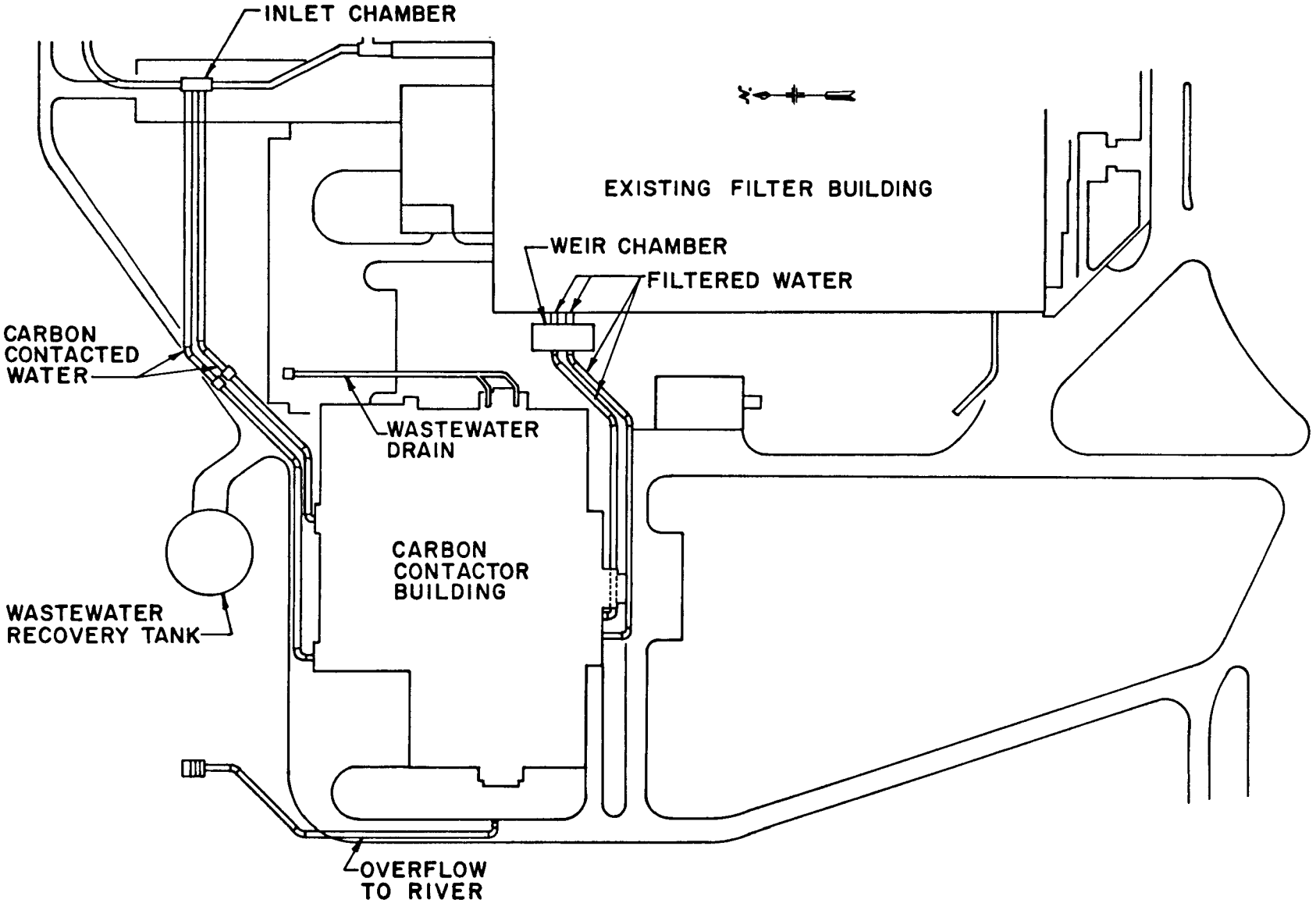
12. Capital Costs

    a. GAC Contactors
    b. Regeneration Equipment
    c. Intermediate Pumping Facilities
    d. Outside Piping
    e. Modification of Existing Facilities

    Capital Cost = $40 Million

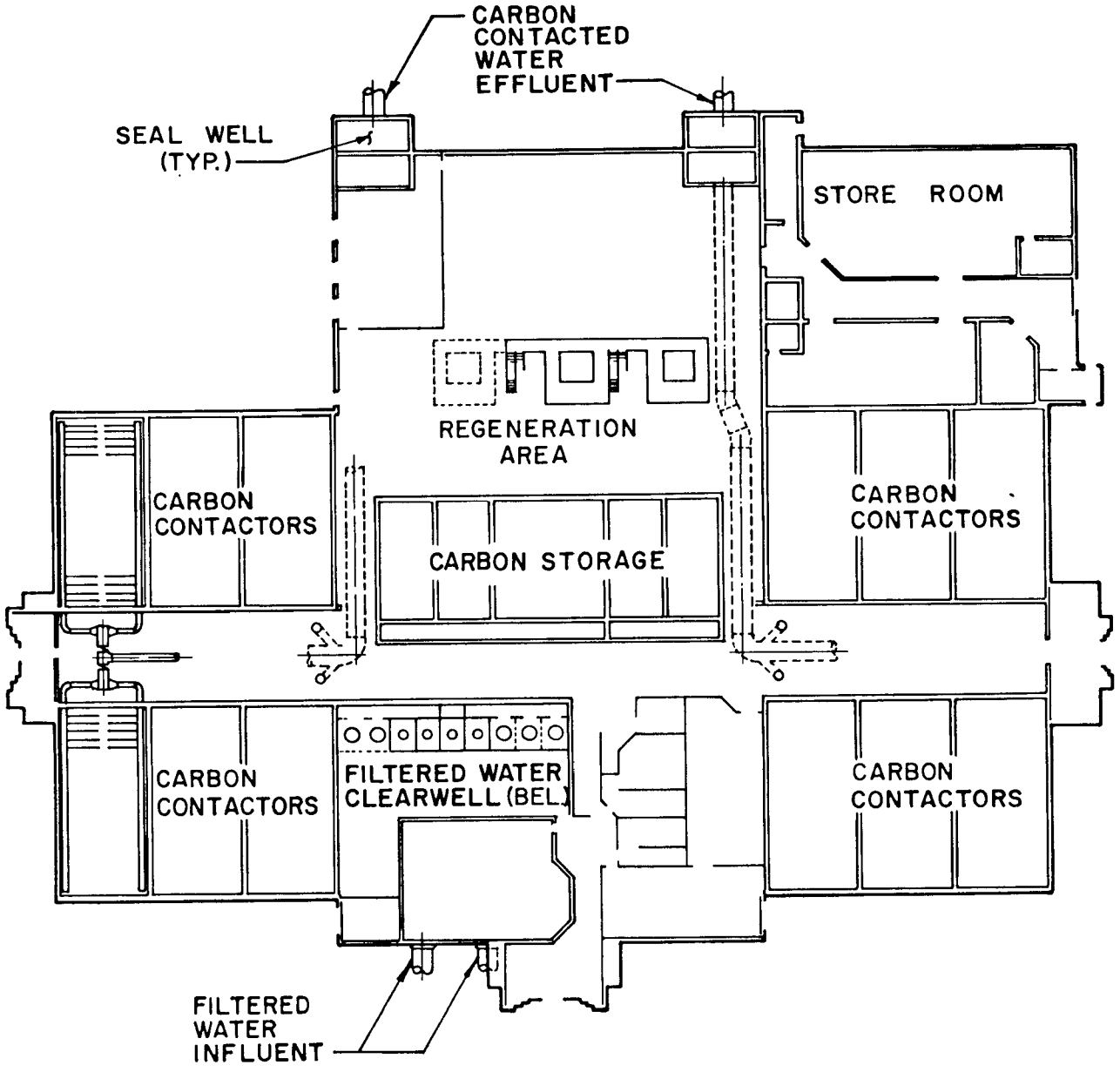
13. O&M Costs

    a. Labor
    b. Power
    c. Natural Gas



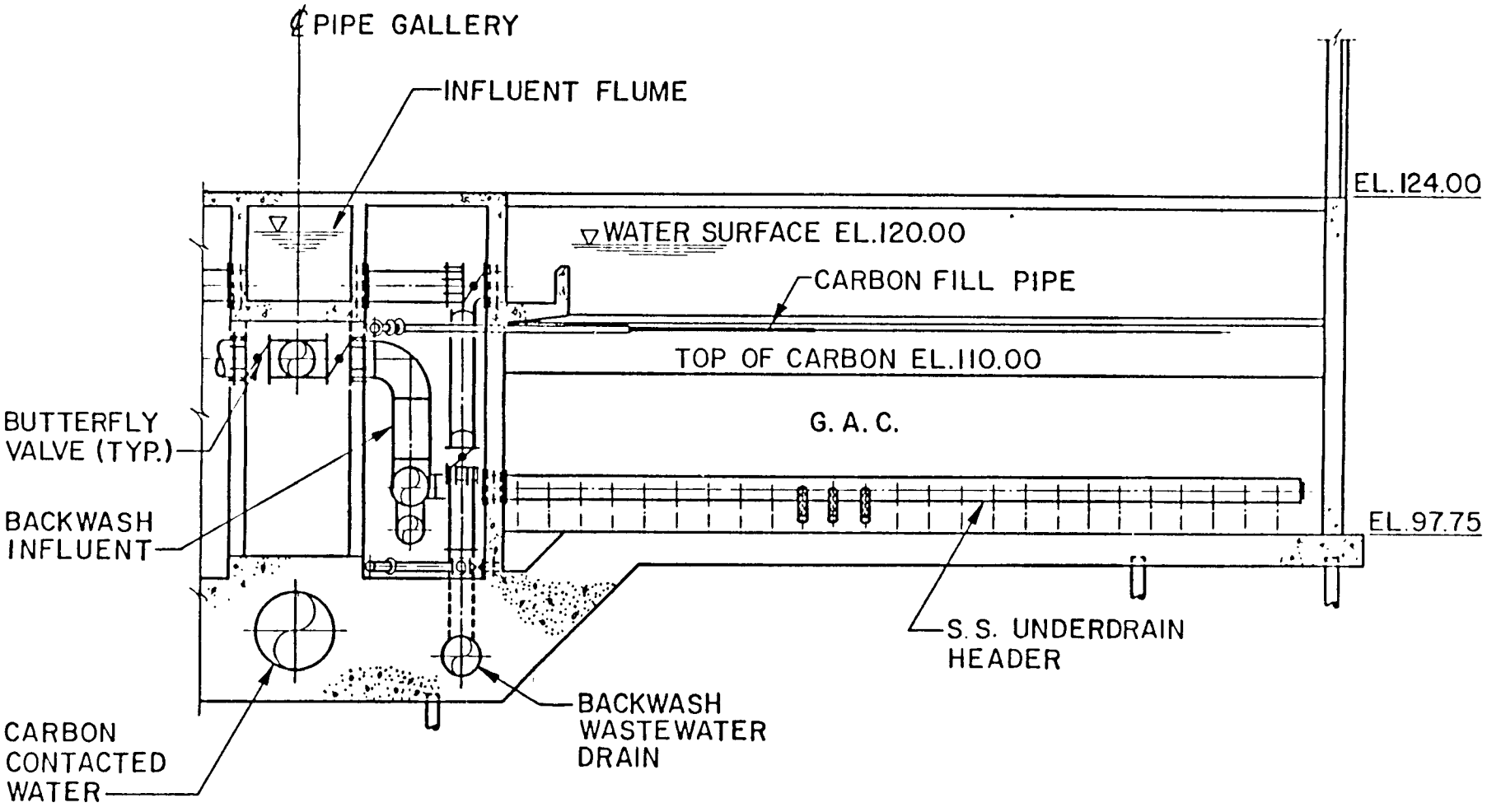
CARBON CONTACTOR BUILDING LAYOUT

FIGURE II-6



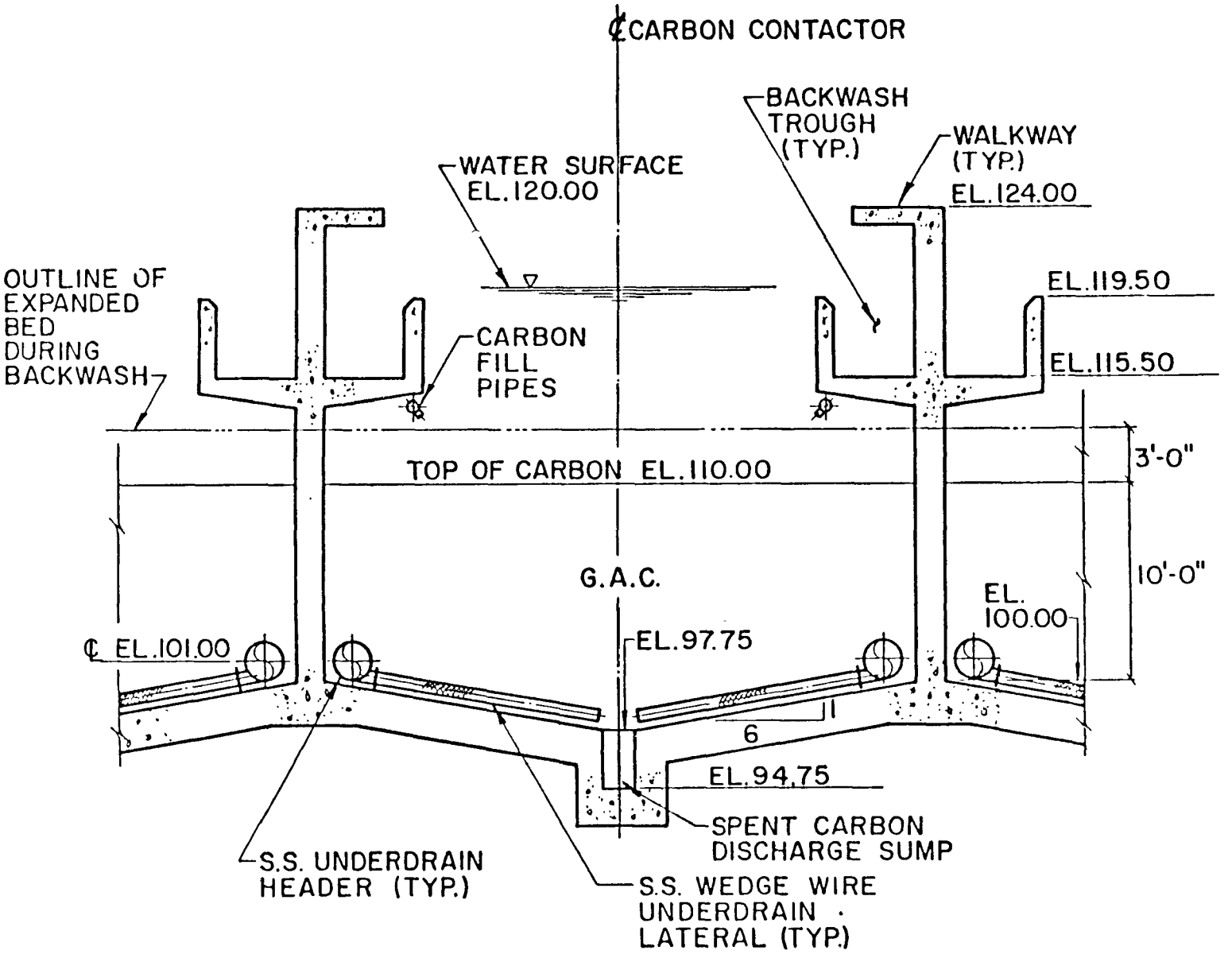
CARBON CONTACTOR BUILDING
FLOOR PLAN

FIGURE II-7



GAC CONTACTOR SECTION

FIGURE II-8



GAC CONTACTOR
CROSS SECTION

FIGURE II-9

REGENERATION SYSTEM SCHEMATIC

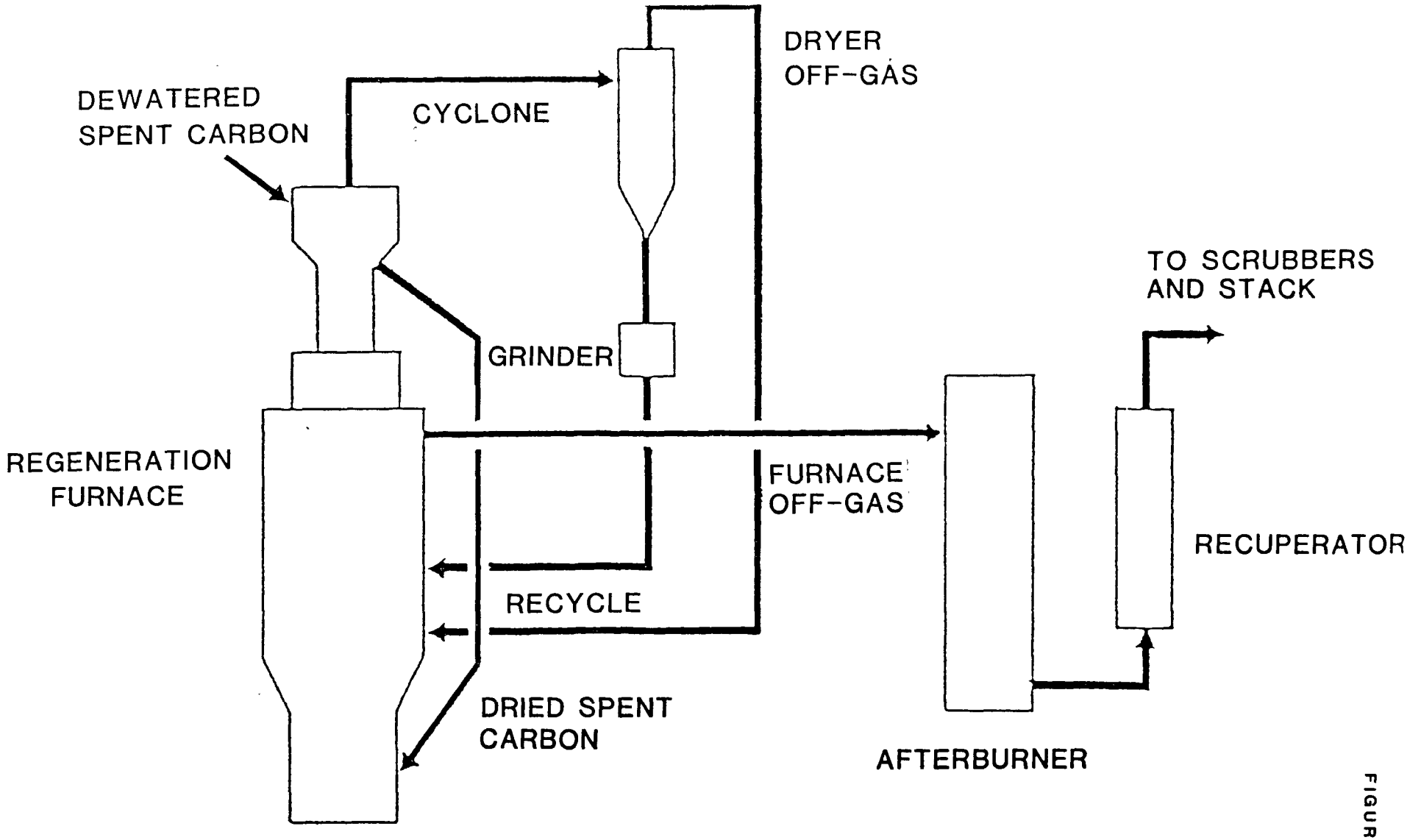


FIGURE II-10

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.

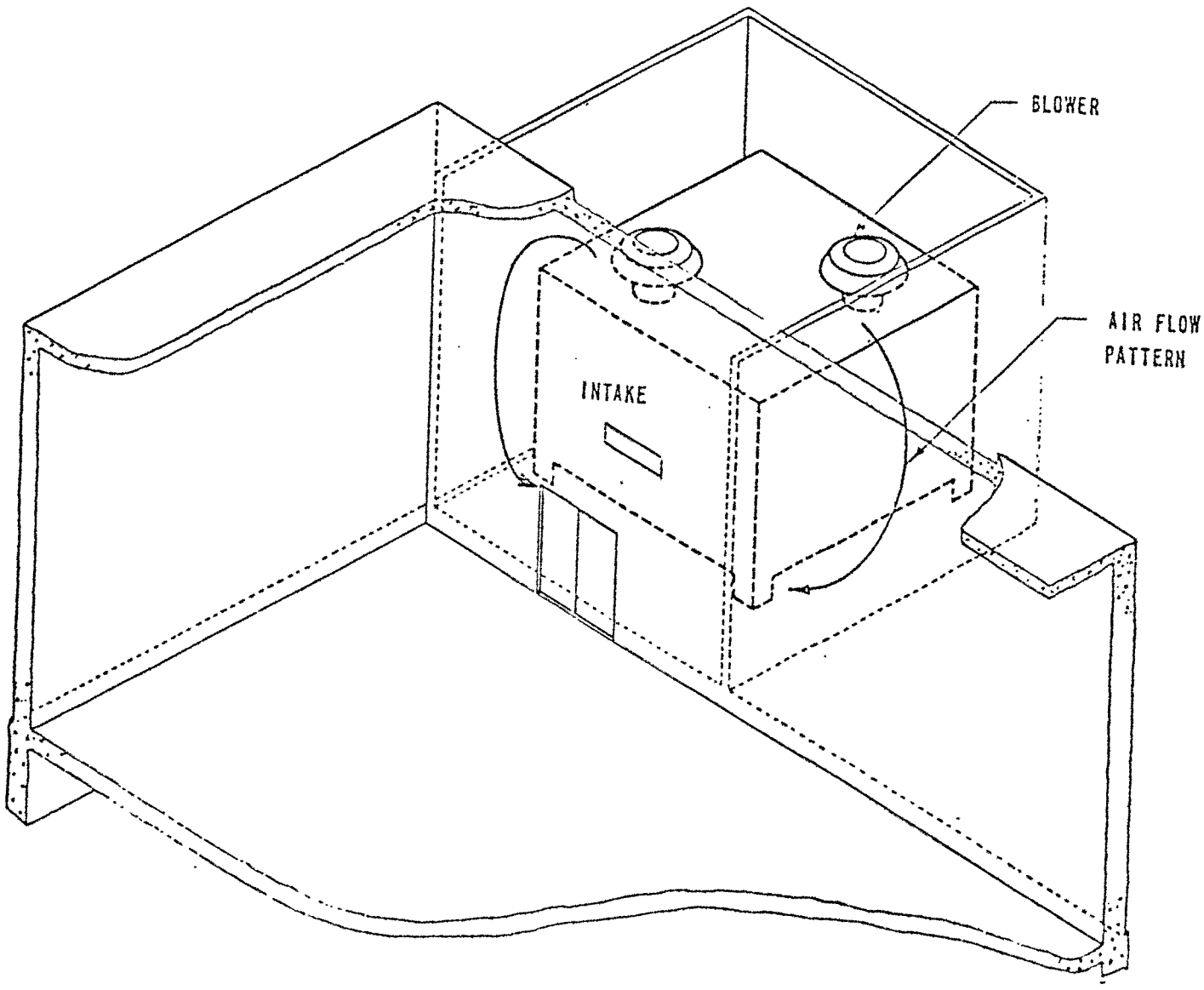
3. Equilibrium concentration follows Henry's Law, which states that the amount of gas that dissolves in a given quantity of liquid, at constant temperature and total pressure, is directly proportional to the partial pressure of the gas above the solution. Henry's constant calculated as follows:

$$H \text{ (dimensionless units)} = \frac{(16.04)(P)(M)}{(T)(S)}$$

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.

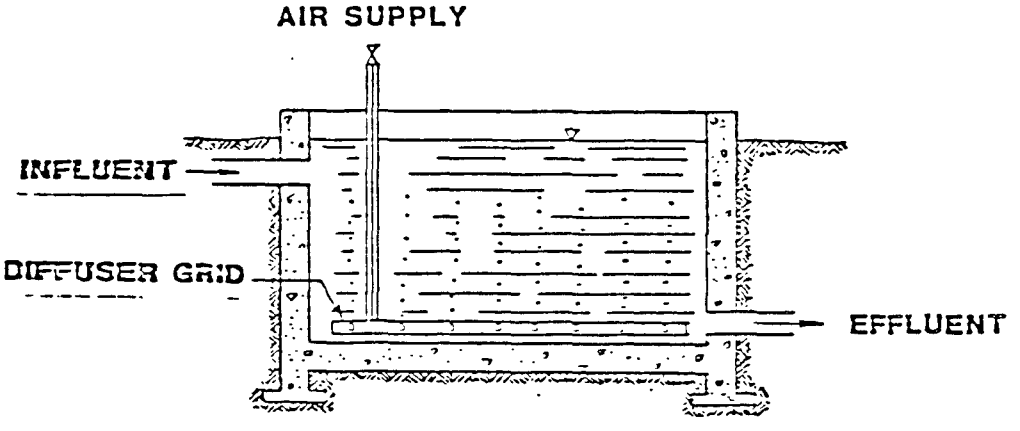
3. Waterfall Aerators

a. Multiple tray - see Figure III-3 for diagram.

b. Packed column - diagram of packed column is shown on Figure III-4.

c. Catenary grid unit - diagram shown on Figure III-5.

d. Higee System - diagram shown on Figure III-6.



DIFFUSED AIR BASIN

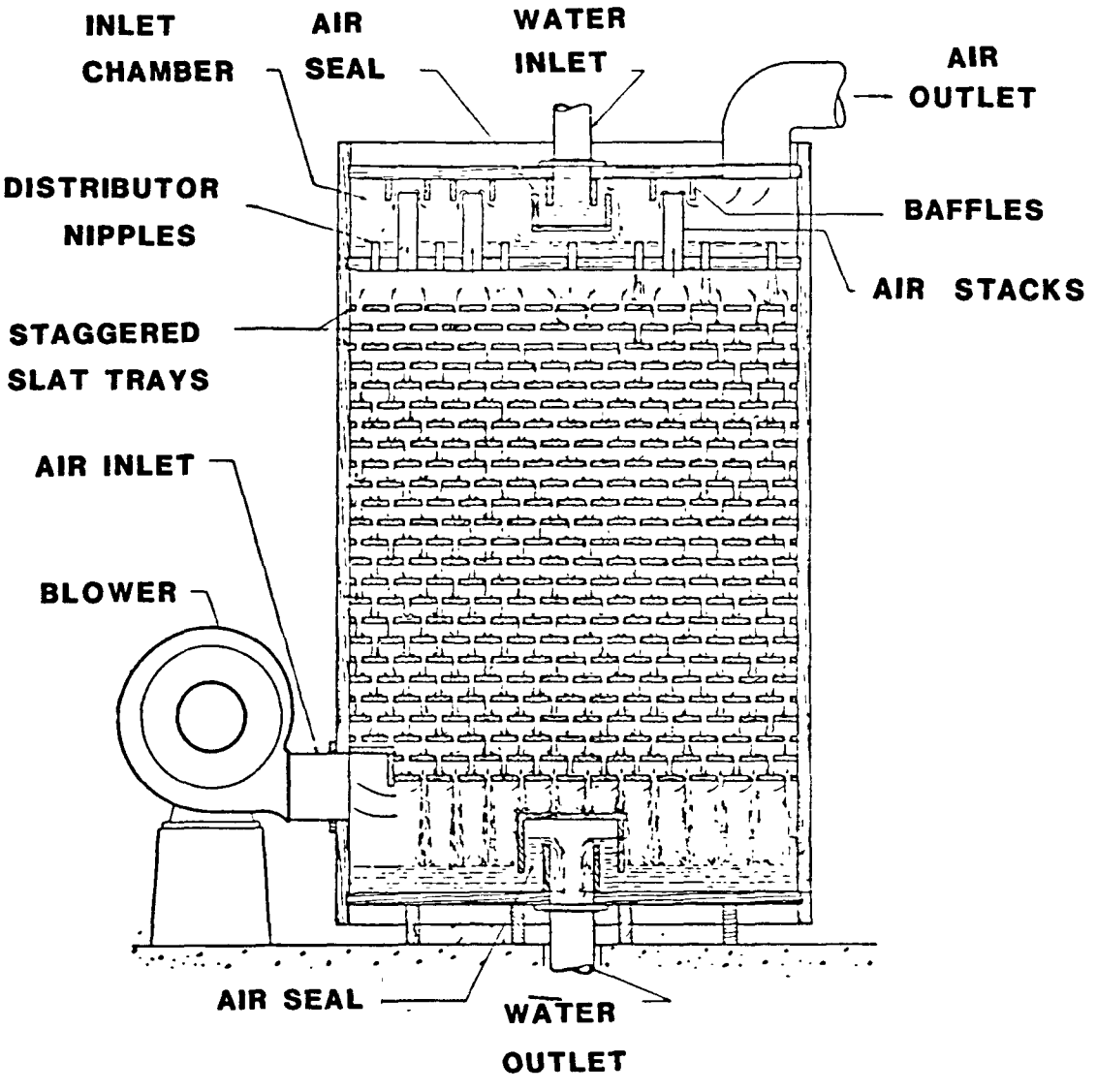


DIAGRAM OF A REDWOOD SLAT TRAY AERATOR

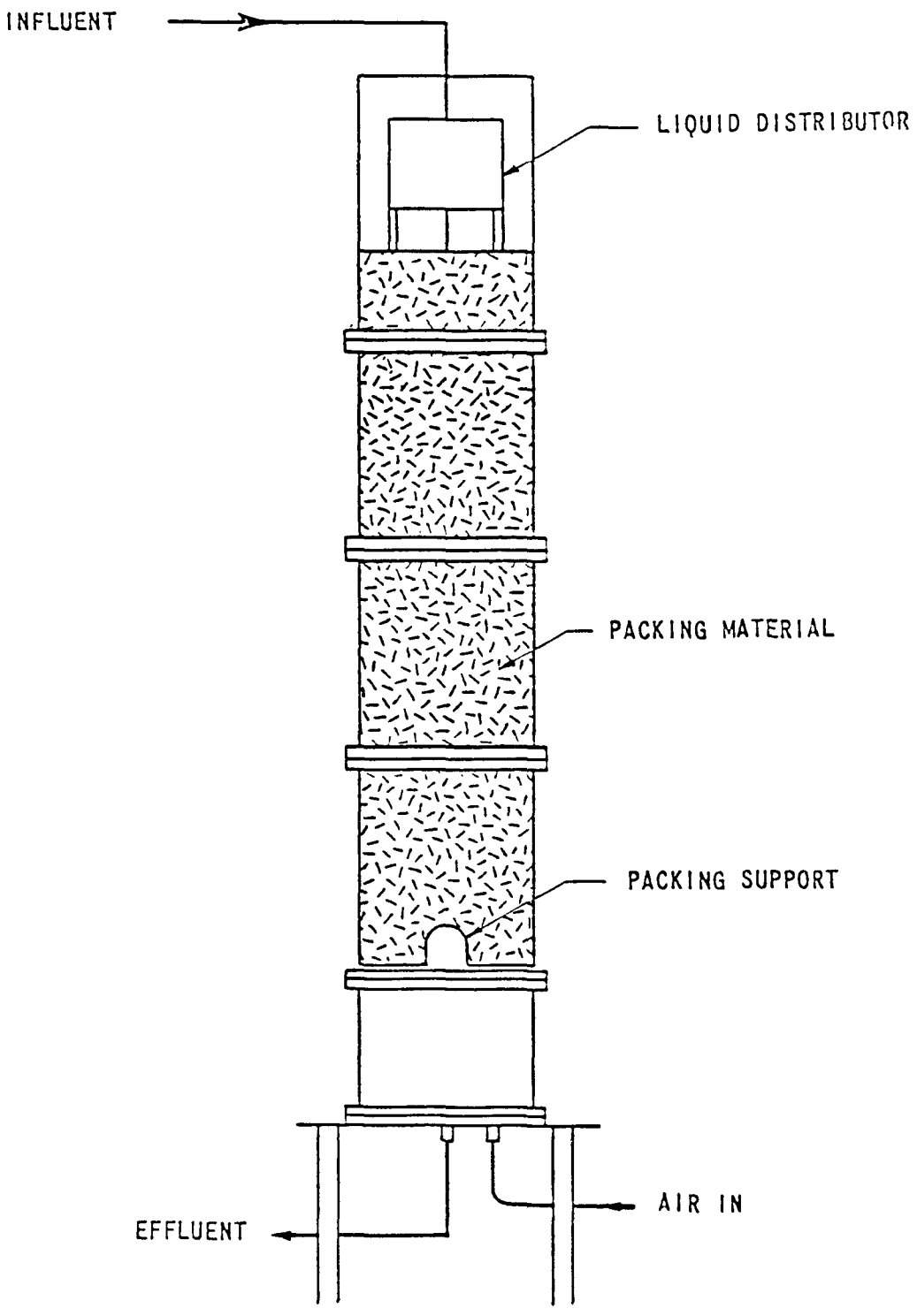
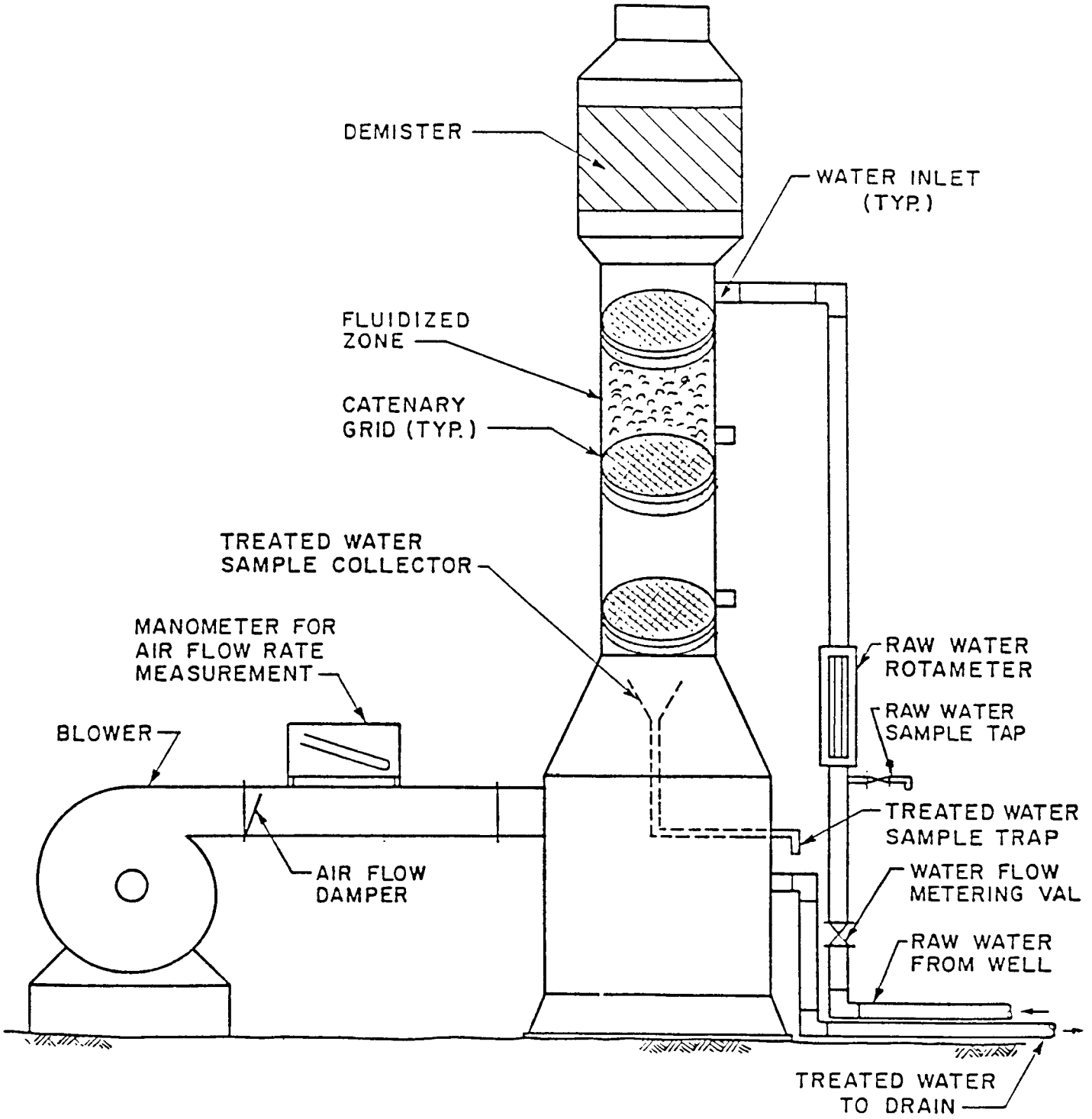
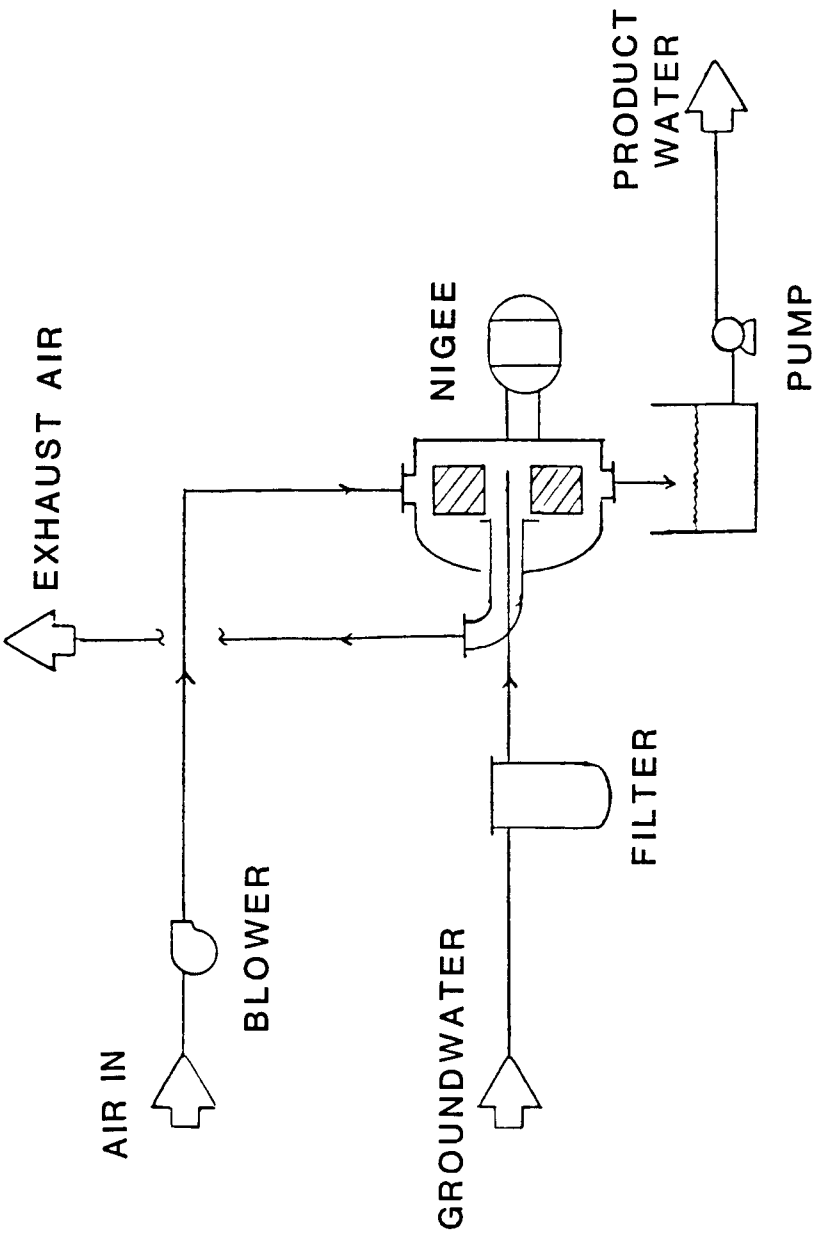


DIAGRAM OF PACKED COLUMN



MALCOLM PIRNIE

DIAGRAM OF PILOT-SCALE
CATENARY GRID UNIT



HIGEE SYSTEM

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

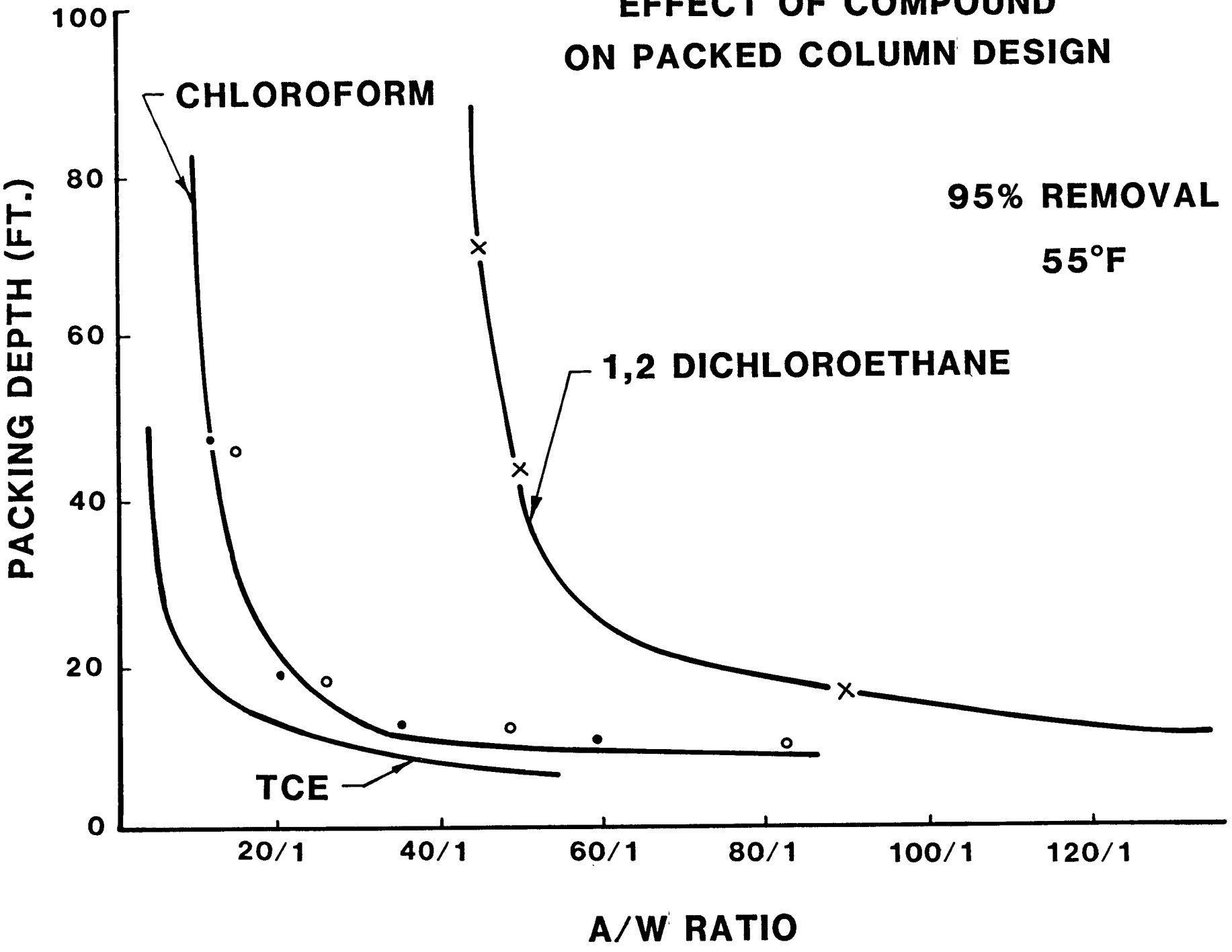
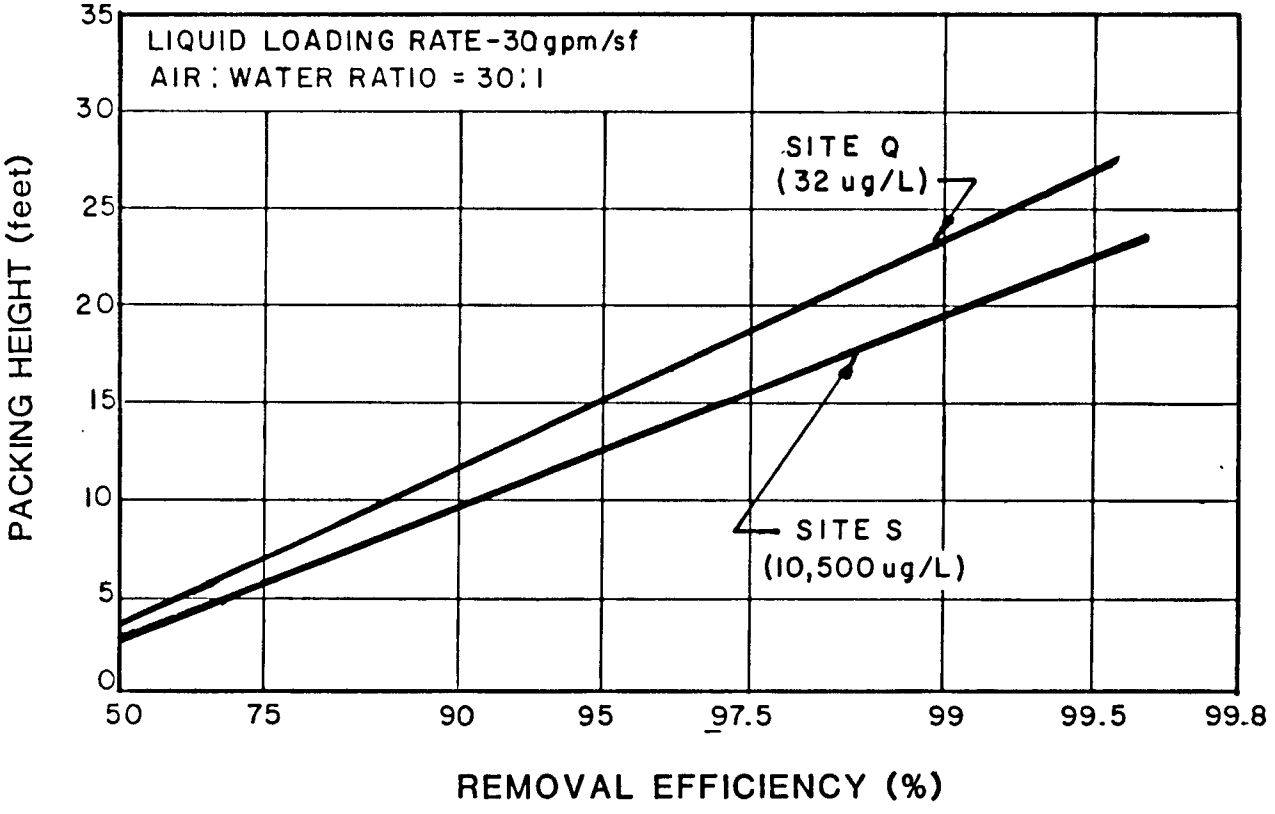

EFFECT OF COMPOUND
ON PACKED COLUMN DESIGN
95% REMOVAL
55°F
CHLOROFORM
1,2 DICHLOROETHANE
TCE
PACKING DEPTH (FT.)
100
80
60
40
20
0
20/1
40/1
60/1
80/1
100/1
120/1
A/W RATIO

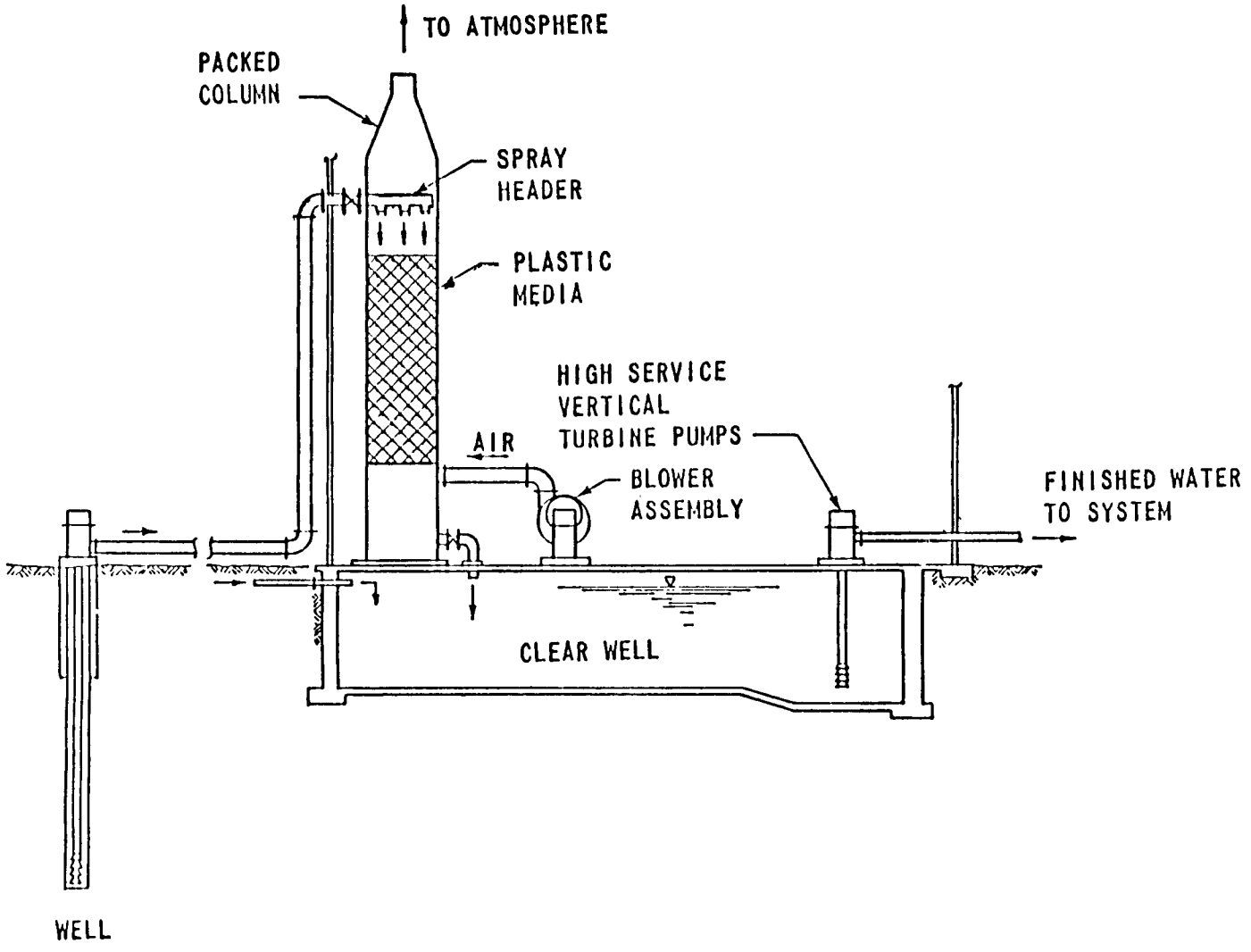
FIGURE III-7



PACKING HEIGHT VS REMOVAL EFFICIENCY

TCE

FIGURE III-8



PACKED COLUMN SYSTEM COMPONENTS

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

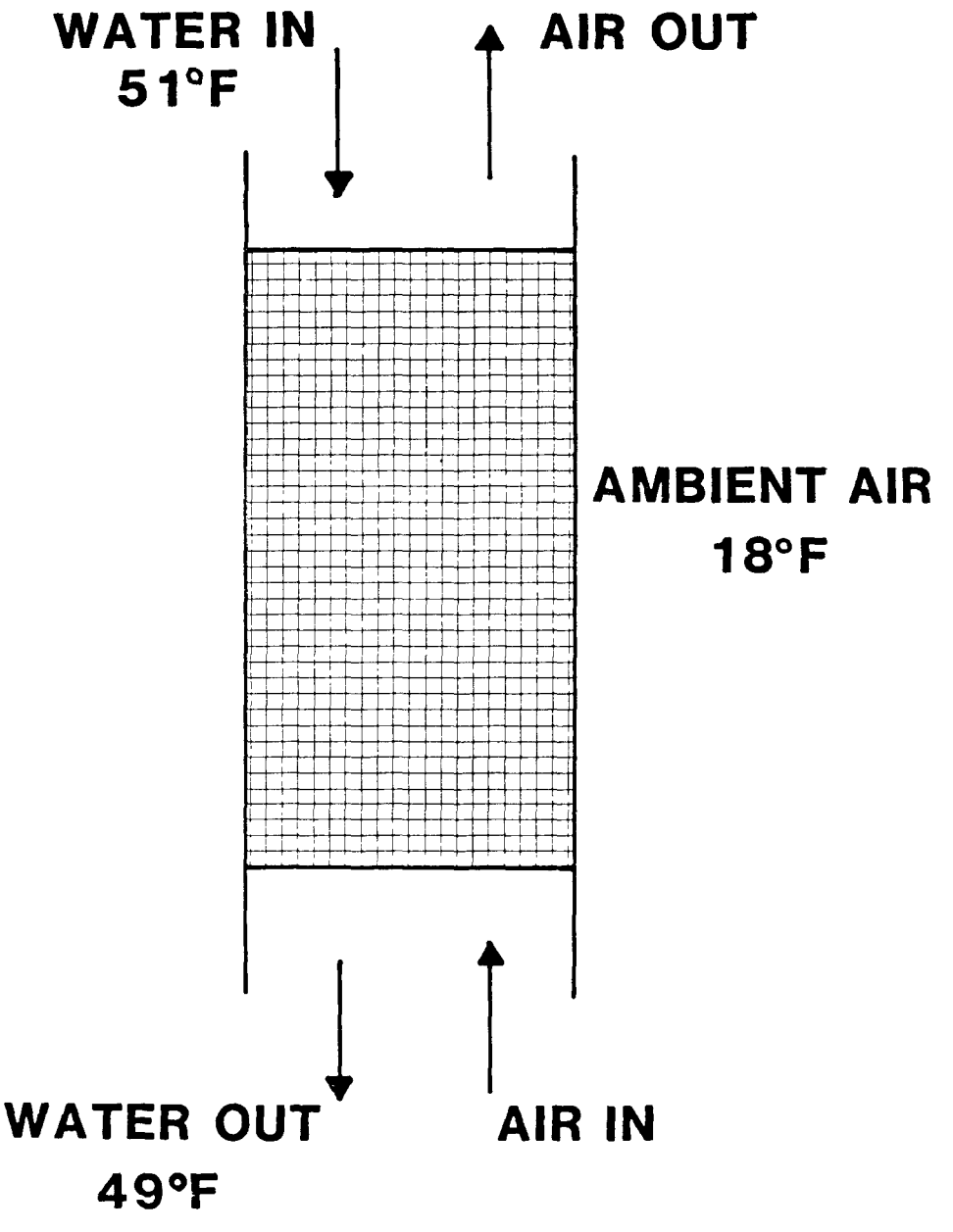
   b. Ambient concentrations

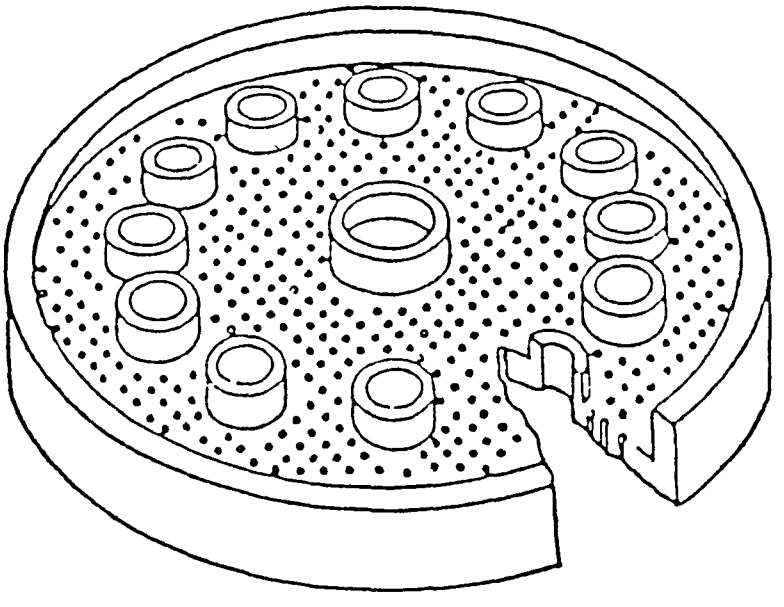
   c. Modeling

   d. Column modifications

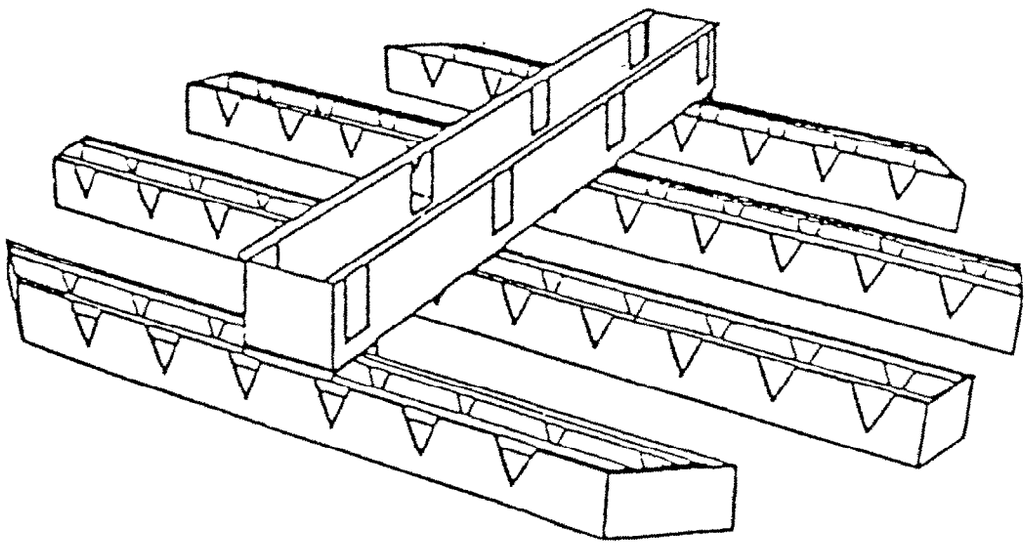
      - Height
      - Air flowrate
      - Exist velocity

TEMPERATURE EFFECTS ON AERATION SYSTEM - JANUARY 1983





Orifice-type distributor



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.

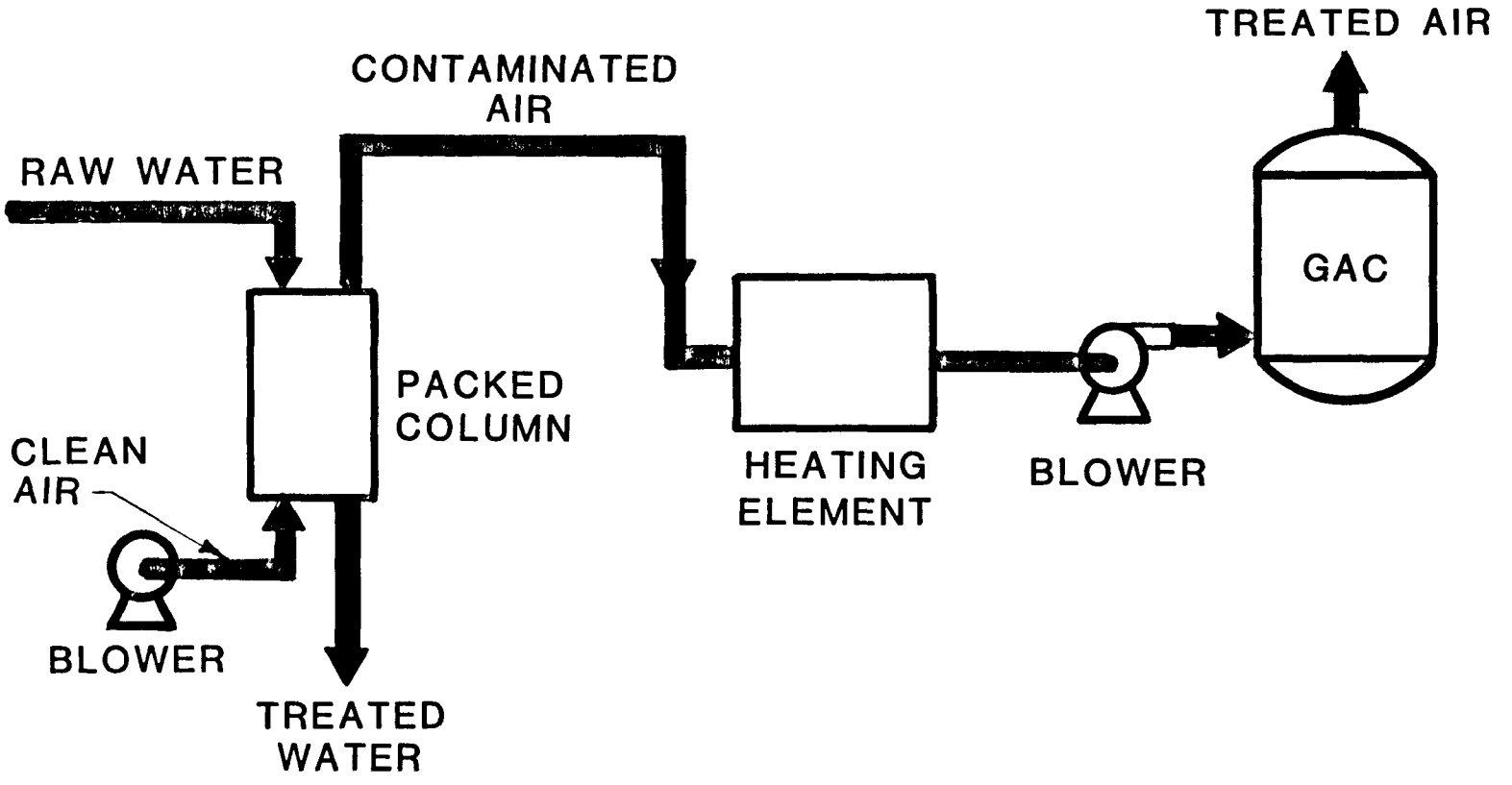
Basic	Site Specific
Column Structure	Special sitework
Internals	Raw water holding tank
Packing	New/restaged well pump
Blower(s)	Blower building
Clearwell	Booster pump building
Booster pump(s)	Chemical facility
Piping	Noise control installation
	Air emissions control

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

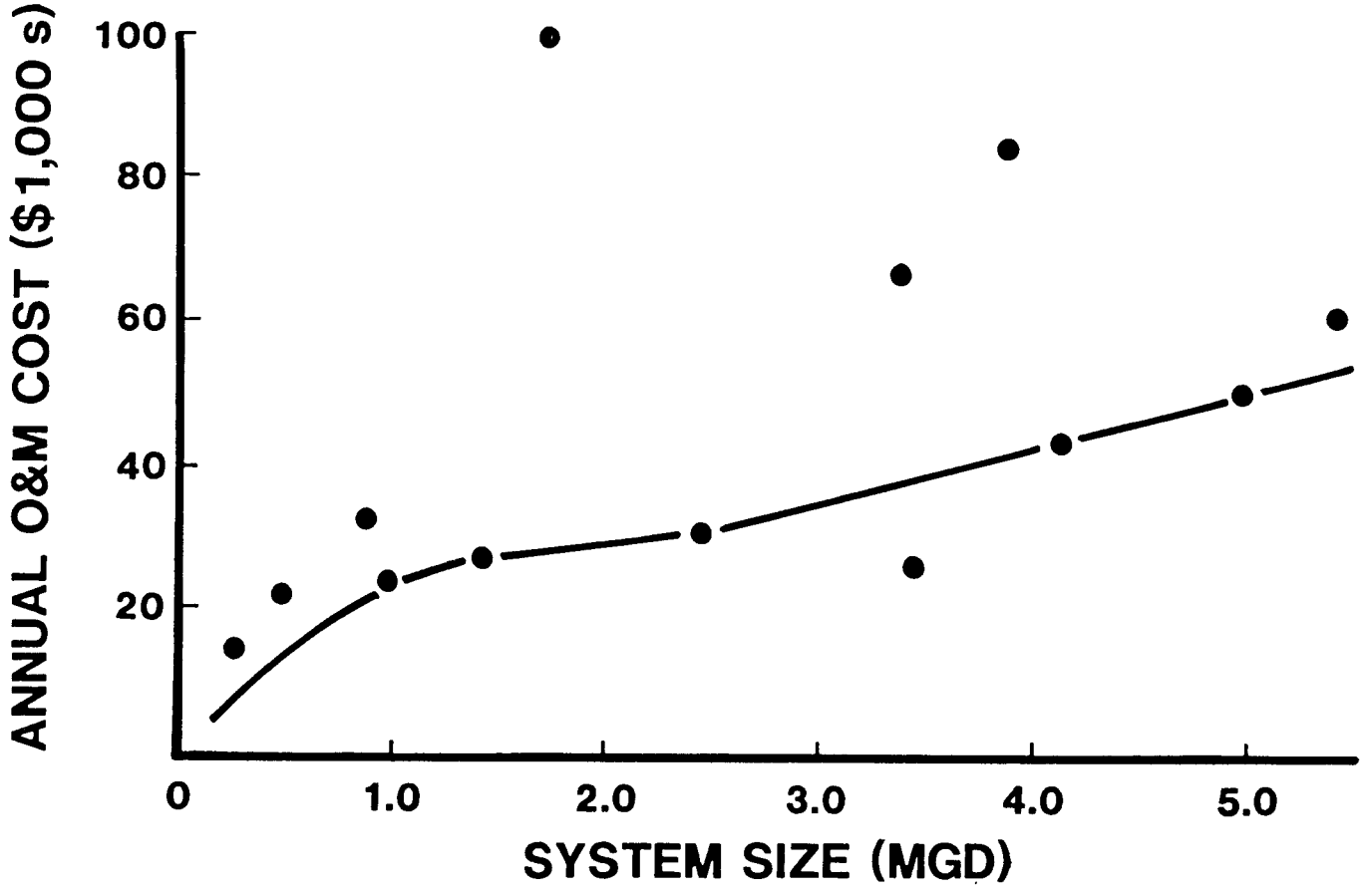


FIGURE III-14

ANNUAL O&M COSTS FOR PACKED COLUMN SYSTEMS

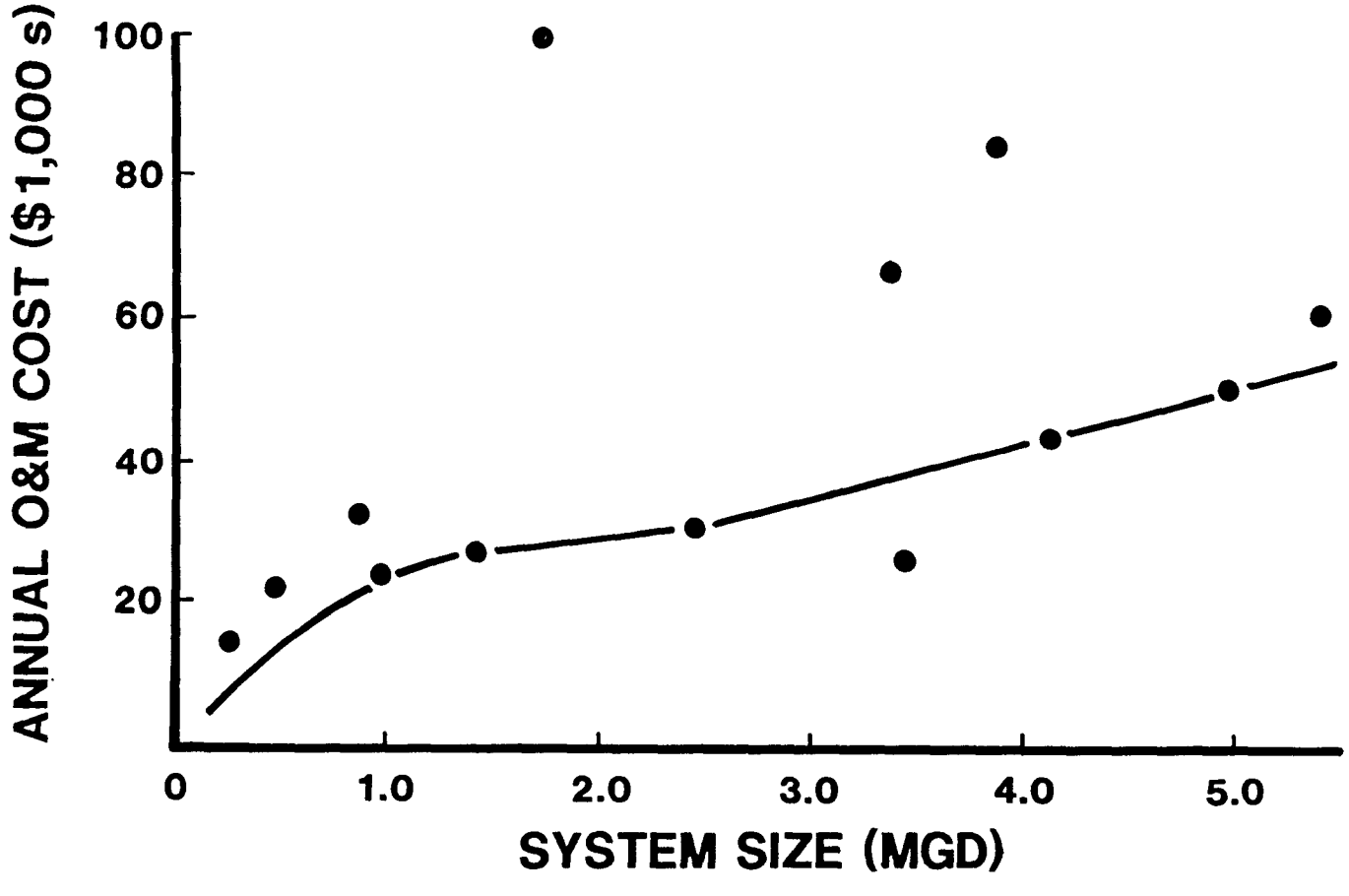


FIGURE III-15

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

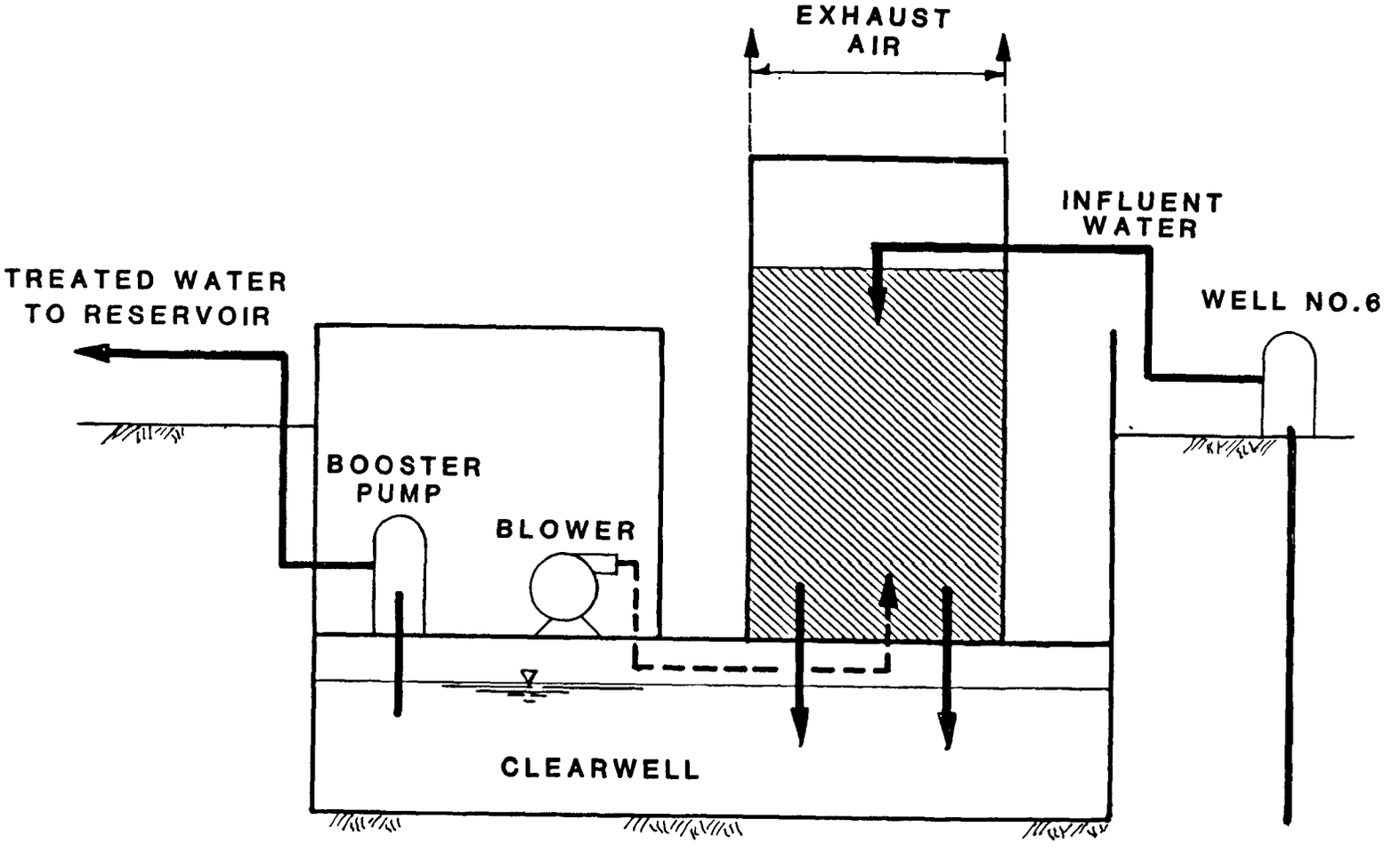
a.	Flow:	1,200 gpm
b.	Packing Height:	12 feet
c.	A:W Ratio:	50:1
d.	Column Diameter:	10 feet
e.	Removal Efficiency:	97 percent of TCE

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



SCHEMATIC DIAGRAM

SCOTTSDALE PACKED COLUMN

FIGURE IV-1

SCOTTSDALE FACILITY LAYOUT

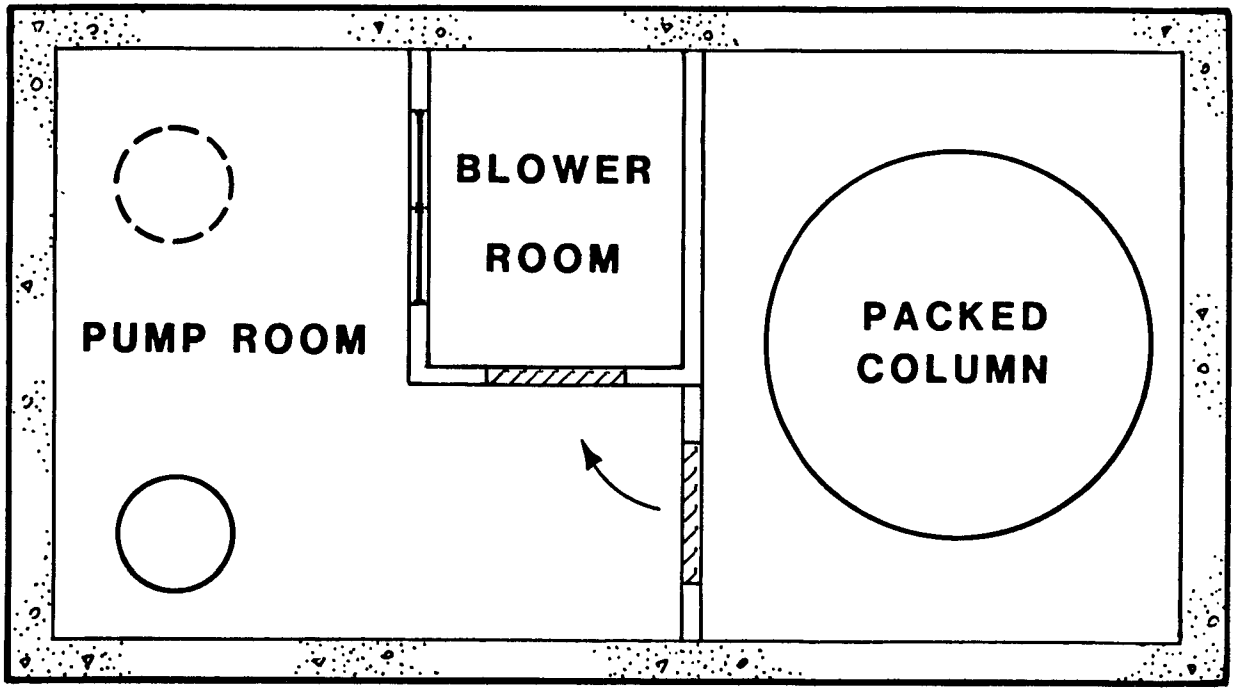


FIGURE IV-2

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

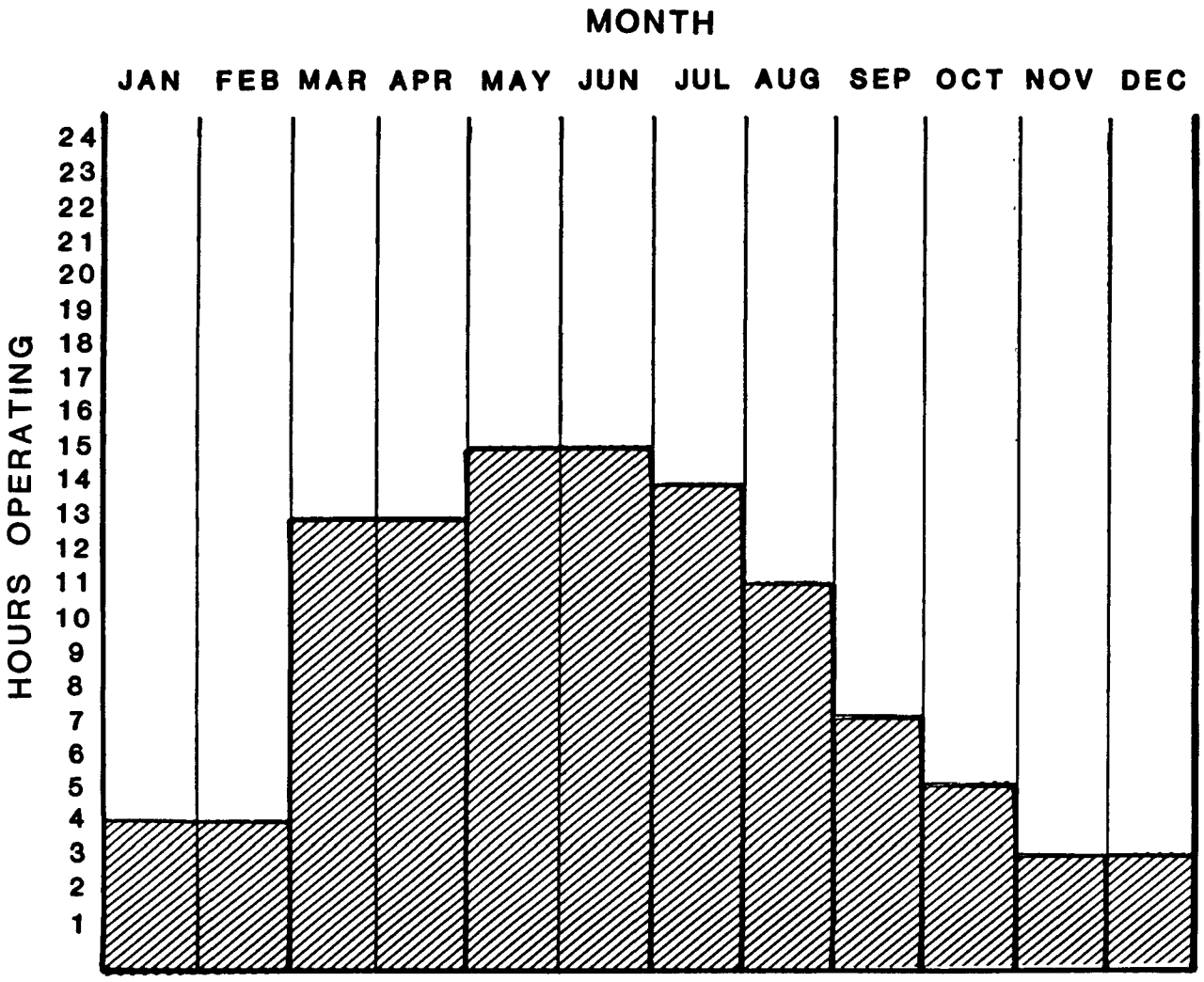


FIGURE IV-3

PART IV

RISK COMMUNICATION

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

- Primary and backup spokesperson
- Inform media and government who spokesperson is - how to contact
- Telephone operators informed how to reach spokesperson
- Establish information gathering teams to report information to spokesperson
- 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

- Rules of the game
- 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:

D) Grab the microphone, ask for a chance to respond and emphatically disagree with her.

PRO: CON:

- Guidelines for success

Dealing with fear

- The problem
- 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:

- 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:

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.

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