XIII. APPENDIX V

REACTIVITY OF THE GLYCIDYL ETHERS

The epoxide group is very reactive and there are several types of chemical reactions in which it will take part. Because glycidyl ethers contain the epoxide group, they would be expected to undergo the types of reactions that have been demonstrated for this moiety. Some reactions that have significance for biologic systems are summarized in Figure XIII-1 [6,98]:

(a) In the presence of hydrogen ions, the epoxide behaves as an ionized, very reactive radical and is capable of multiple additive reactions on the electronegative radicals. The epoxide ring is cleaved, and an alcohol (hydroxyl group) is formed.

(b) With organic acids, the alcohol is formed and an esterification takes place.

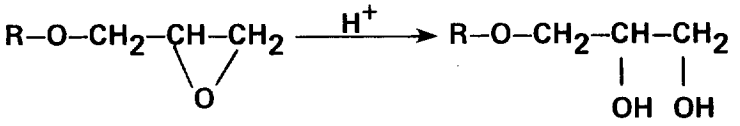
(c) Phenols react to form the alcohol and the aromatic ring attaches through the ether linkage.

(d) Some nucleophilic compounds react directly on the epoxide, cleaving the ring and making the oxygen electronegative. If the R group is nucleophilic, the effect is stronger.

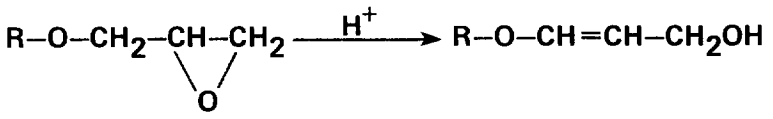
(e) The epoxides are also described as alkylating agents or electrophilic agents, which are postulated to form a carbonium ion in which the positive charge resides on one of the carbon atoms [6]. The carbonium ion reacts with water or with nucleophilic compounds such as proteins and nucleic acids [6].

(a) Alcohol Formation

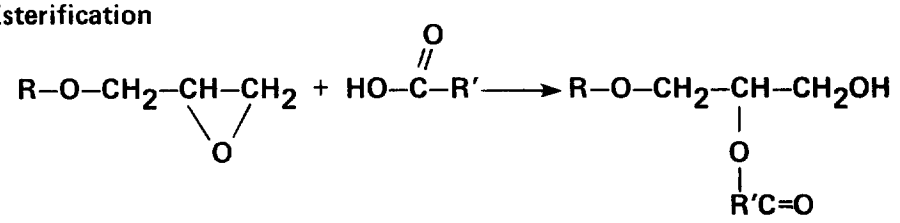
aqueous



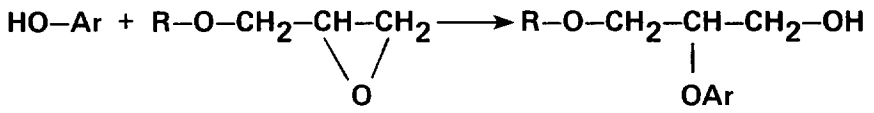
nonaqueous



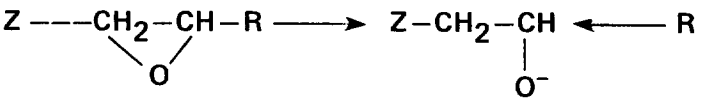
(b) Esterification



(c) Phenolic Reaction



(d) Reaction with Nucleophilic Substance (Z)



(e) Carbonium Ion Formation

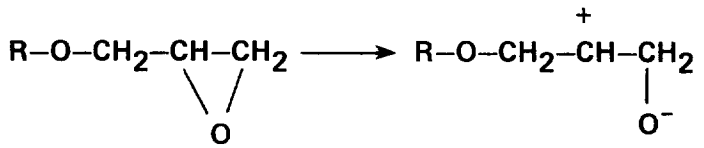


FIGURE XIII-1

BIOLOGICALLY IMPORTANT REACTIONS OF EPOXIDES

Adapted from references 6,98

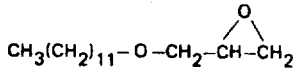
Experimental evidence also indicates that glycidyl ethers are very reactive biologically. They have been used for tumor inhibition because of their alkylating properties [52]. They have produced chromosomal aberrations in plants [6,53-55], and Hine et al [41,48] have demonstrated their radiomimetic effects on blood cells. BGE has been shown to be mutagenic in mammals [58], and all glycidyl ethers tested have shown some mutagenic activity in bacterial systems [49,57,58]. However, very high doses were generally required to produce these effects and attempts to find consistent structure-activity relationships among various glycidyl ethers have met with little success [48,56].

XIV. TABLES AND FIGURE

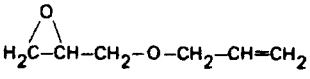
TABLE XIV-1

SYNONYMS AND STRUCTURAL FORMULAS FOR SOME GLYCIDYL ETHERS

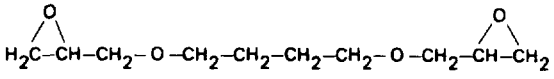
Alkyl glycidyl ether (C12)
*Oxirane, (methoxydodecyl)-
Lauryl glycidyl ether
Aliphatic glycidyl ether



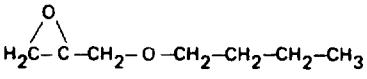
Allyl glycidyl ether (AGE)
*Oxirane, [(2-propenyloxy)methyl]-
Allyl 2,3-epoxypropyl ether
1,2-Epoxy-3-allyloxypropane



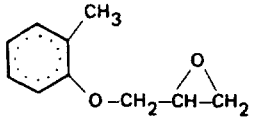
1,4-Butanediol diglycidyl ether
*Oxirane, 2,2'[1,4-butanediol bis(oxymethylene]bis-
Butane-1,4-diol diglycidyl ether
1,4-Bis-(2,3-epoxypropoxy)butane



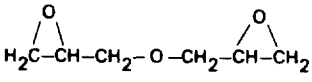
n-Butyl glycidyl ether (BGE)
*Oxirane, (butoxymethyl)-
Glyceryl butyl ether
1-Butoxy-2,3-epoxypropane
Butyl 2,3-epoxypropyl ether
2,3-Epoxypropyl ether of butanol-1



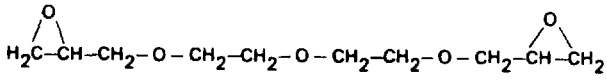
o-Cresyl glycidyl ether (CGE)
*Oxirane, [(2-methylphenoxy)methyl]-
Glycidyl o-tolyl ether
2,3-Epoxypropyl-o-tolyl ether



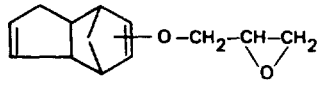
Di(2,3-epoxypropyl) ether (DGE)
*Oxirane, 2,2'[oxy-bis(methylene)]bis-
Diglycidyl ether
Bis(2,3-epoxypropyl) ether
Glycidyl ether
Diallyl ether dioxide



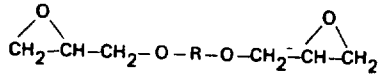
Diethylene glycol diglycidyl ether



Dicyclopentadiene glycidyl ether



Diglycidyl ether of substituted glycerin

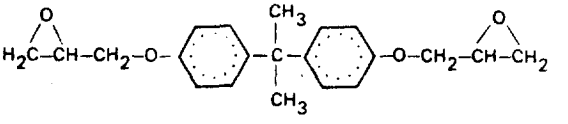


R = aliphatic radicals (average mw 100)

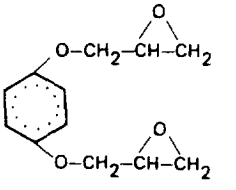
TABLE XIV-1 (CONTINUED)

SYNONYMS AND STRUCTURAL FORMULAS FOR SOME GLYCIDYL ETHERS

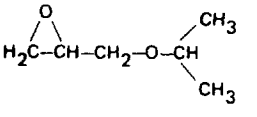
Diphenylol propane diglycidyl ether
*Oxirane, 2,2'-[(1-methylethylidene) bis(4,1-phenylene oxymethylene)]bis-
Diglycidyl ether of bisphenol A
2,2-Bis[p-(2,3-epoxypropoxy)phenyl]-propane
2,2-Bis(4-hydroxyphenyl)propane diglycidyl ether
Diomethane diglycidyl ether
2,2-Bis[p-(glycidoxy)phenyl]propane



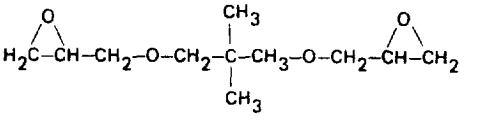
Hydroquinone diglycidyl ether
*Oxirane, 2,2'-[1,4-phenylene) bis(oxymethylene)]bis-
Hydroquinone bis(2,3-epoxypropyl)ether
1,4-Bis(2,3-epoxypropoxy)benzene



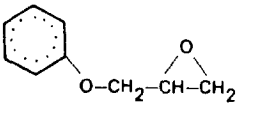
Isopropyl glycidyl ether (IGE)
*Oxirane, [(1-methylethoxy)methyl]-
3-Isopropoxy-1,2-epoxy propane
(Isopropoxymethyl)oxirane



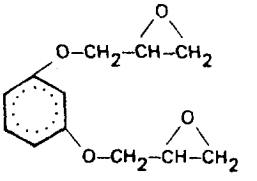
Neopentyl glycol diglycidyl ether
*Oxirane, 2,2'[1,3-(2,2-dimethyl) propane diyl bis(oxymethylene'] bis-



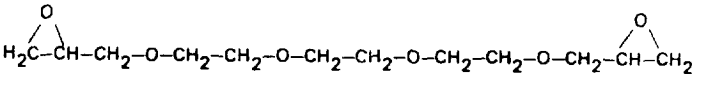
Phenyl glycidyl ether (PGE)
*Oxirane, (phenoxymethyl)-
Gamma-phenoxypropylene oxide
Phenoxypropenoxide
2,3-Epoxypropyl phenyl ether



Resorcinol diglycidyl ether
*Oxirane, 2,2'-[1,3-phenylene bis(oxymethylene)]2 bis-
1,3-Bis(2,3-epoxypropoxy)benzene
Resorcinol bis-2,3-epoxypropyl ether



Triethylene glycol diglycidyl ether
Ethoglucid
Etoglucid
Epodyl



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*IUPAC name

TABLE XIV-2

PHYSICAL AND CHEMICAL PROPERTIES OF SELECTED GLYCIDYL ETHERS

Allyl Glycidyl Ether	
Empirical formula	C6H10O2
Formula weight	114.14
Appearance and odor	Colorless liquid; characteristic but not unpleasant odor
Boiling point	153.9 C (760 mmHg)
Freezing point	Forms glass at -100 C
Vapor density (air = 1)	3.32 (25 C)
Specific gravity (water = 1.0 at 4 C)	0.9698 (20 C)
Vapor pressure	4.7 mmHg (25 C)
% in saturated air	0.62 (25 C)
Refractive index	1.4348 (20 C)
Solubility	
In water	14.1%
In other solvents	Miscible with acetone, toluene, and octane
Flashpoint	57.2 C
Conversion factors (760 mmHg and 25 C)	1 mg/cu m = 0.214 ppm 1 ppm = 4.67 mg/cu m
n-Butyl Glycidyl Ether	
Empirical formula	C7H14O2
Formula weight	130.21

TABLE XIV-2 (CONTINUED)

PHYSICAL AND CHEMICAL PROPERTIES OF SELECTED GLYCIDYL ETHERS

n-Butyl Glycidyl Ether (continued)	
Appearance and odor	Colorless liquid; slight, irritant odor
Boiling point	164 C (760 mmHg)
Vapor density (air = 1)	3.78 (25 C)
Specific gravity (water = 1 at 4 C)	0.9087 (25 C)
Vapor pressure	3.2 mmHg (25 C)
% in saturated air	0.42 (25 C)
Solubility	2% in water (20 C)
Conversion factors (760 mmHg and 25 C)	1 mg/cu m = 0.188 ppm 1 ppm = 5.32 mg/cu m
o-Cresyl Glycidyl Ether	
Empirical formula	C10H12O2
Formula weight	164.21
Flashpoint	121.1 C
Viscosity C 25 C	20 cps
Epoxide equivalent weight	180
Conversion factors (760 mm Hg and 25 C)	1 mg/cu m = 0.149 ppm 1 ppm = 6.72 mg/cu m

TABLE XIV-2 (CONTINUED)

PHYSICAL AND CHEMICAL PROPERTIES OF SELECTED GLYCIDYL ETHERS

Di(2,3-epoxypropyl) Ether

Empirical formula	C6H10O3
Formula weight	130.1
Appearance and odor	Colorless liquid; pronounced, irritant odor
Boiling point	260 C (760 mmHg)
Vapor density (air = 1)	3.78 (25 C)
Specific gravity (water = 1.0 at 4 C)	1.262 (25 C)
Vapor pressure	0.09 mmHg (25 C)
% in saturated air	0.0121 (25 C)
Flashpoint	64 C
Conversion factors (760 mmHg and 25 C)	1 mg/cu m = 0.188 ppm 1 ppm = 5.32 mg/cu m

TABLE XIV-2 (CONTINUED)

PHYSICAL AND CHEMICAL PROPERTIES OF SELECTED GLYCIDYL ETHERS

Isopropyl Glycidyl Ether	
Empirical formula	$C_6H_{12}O_2$
Formula weight	116.16
Appearance	Colorless liquid
Boiling point	137 C (760 mmHg)
Vapor density	4.15 (25 C)
Specific gravity (water = 1.0 at 4 C)	0.9186 (20 C)
Vapor pressure	9.4 mmHg (25 C)
% in saturated air	1.237 (25 C)
Solubility	
In water	18.8%
In other solvents	Soluble in ketones and alcohols
Conversion factors (760 mmHg and 25 C)	1 mg/cu m = 0.210 ppm 1 ppm = 4.75 mg/cu m
Phenyl Glycidyl Ether	
Empirical formula	$C_9H_{10}O_2$
Formula weight	150.17
Appearance	Colorless liquid
Boiling point	245 C (760 mmHg)
Melting point	3.5 C
Vapor density (air = 1)	4.37 (25 C)
Specific gravity (water = 1.0 at 4 C)	1.1092 (20 C)

TABLE XIV-2 (CONTINUED)

PHYSICAL AND CHEMICAL PROPERTIES OF SELECTED GLYCIDYL ETHERS

Phenyl Glycidyl Ether (continued)	
Vapor pressure	0.01 mmHg (25 C)
Refractive index	1.5314
% in saturated air	0.0013 (25 C)
Solubility	
In water	0.24%
In other solvents	12.9% in octane; completely soluble in acetone and toluene
Conversion factors (760 mmHg and 25 C)	1 mg/cu m = 0.163 ppm 1 ppm = 6.14 mg/cu m
Resorcinol Diglycidyl Ether	
Empirical formula	C12H1404
Formula weight	222.24
Appearance and odor	Colorless solid; slight, phenolic odor
Boiling points	150-160 C (0.05 mmHg) 208-210 C (12 mmHg)
Melting point	32-33 C
Vapor density (air = 1)	7.95
Specific gravity (water = 1.0 at 4 C)	1.2183 (20 C)
Refractive index	1.5409 (20 C)
Conversion factors (760 mmHg and 4 C)	1 mg/cu m = 0.110 ppm 1 ppm = 9.09 mg/cu m

TABLE XIV-2 (CONTINUED)

PHYSICAL AND CHEMICAL PROPERTIES OF SELECTED GLYCIDYL ETHERS

Triethylene Glycol Diglycidyl Ether

Empirical formula	C12H2206
Formula Weight	262.31
Appearance	Liquid
Boiling points	133-149 C (0.1 mmHg) 195-197 C (2 mmHg)
Melting point	-15 to -11 C
Specific gravity (water = 1.0 at 4 C)	1.1312 (20 C)
Refractive index	1.4622 (20 C)
Solubility	Miscible with water
Flashpoint	79.4 C
Conversion factors (760 mmHg and 25 C)	1 mg/cu m = 0.093 ppm 1 ppm = 10.73 mg/cu m

Adapted from references 1-5

TABLE XIV-3

OCCUPATIONS WITH POTENTIAL EXPOSURE TO GLYCIDYL ETHERS

Adhesive makers and users
Automobile workers
Cable makers
Casting and molding workers
Custom-blended epoxy resin system production workers
Dental laboratory technicians
Dentists
Electrical appliance production workers
Electronic equipment production workers
Flooring makers
Laminators
Glycidyl ether production workers
Nurses
Paintmakers
Physicians
Polyglycidyl ether production workers
Soft drink canners
Telephone production workers
Telephone installers

Adapted from references 17,19-22

TABLE XIV-4

ACUTE TOXICITY OF GLYCIDYL ETHERS

Compound	LD50 (g/kg)						LC50 (mg/cu m)		Reference
	Oral			SC	Dermal		8-hr	4-hr	
	Rat	Mouse	Rabbit	Mouse	Rat	Rabbit	Rat	Mouse	
AGE	1.60	0.39	-	-	-	2.55	3,120	1,260	23
BGE	3.43	-	-	-	-	2.26	-	-	32
"	2.26	1.53	-	-	-	4.93	5,480	>18,600	23
"	2.05	-	-	-	-	2.52	-	-	37
"	2.5	-	-	-	-	-	-	-	30
CGE	-	-	-	0.96	-	-	-	-	36
DGE	0.45	0.17	-	-	-	1.5	>1,060	160	23
IGE	4.20	1.30	-	-	-	9.65	5,220	7,120	23
PGE	3.85	1.40	-	-	-	2.99	>60	>60	23
"	4.26	-	-	-	-	1.50	-	-	34
"	2.6-3.8	-	-	-	2.16	-	-	-	35
"	-	-	-	0.76	-	-	-	-	36
Alkyl glycidyl ether (C8-C10)	9.4	-	-	-	-	-	-	-	30
Alkyl glycidyl ether (C12-C14)	17.1	-	-	-	-	-	-	-	30
Butanediol diglycidyl ether	2.98	-	-	-	-	1.3	-	-	32
Diphenylol propane diglycidyl ether	21.6	-	-	-	-	>22	-	-	37
Resorcinol diglycidyl ether	2.57	0.98	1.24	-	-	-	-	-	33

TABLE XIV-5

DEGREE OF IRRITATION* PRODUCED IN RABBITS
BY TOPICAL APPLICATION OF UNDILUTED GLYCIDYL ETHERS

Compound	Skin		Eyes	Reference
	Single Application (24 hr)	Repeated Application (1 hr x 5-7 d)	Single Application	
AGE	Moderate (4.0/8)	Moderate (3.8/8)	Severe (72/110)	23
BGE	Severe (8.0/8)	--	Moderate (23.2/110)	30
"	Moderate (2.8/8)	Moderate (3.8/8)	Mild (4/110)	23
"	Moderate (5/10)	--	Mild (4/10)	32
"	Mild	--	Moderate (5/10)	37
"	"	--	--	42
DGE	Severe (7.5/8)	Severe (6.5/8)	Severe (74/110)	23, 41
IGE	Moderate (4.3/8)	Moderate (2.2/8)	Moderate (40/110)	23
PGE	Severe	--	Severe**	35
"	Moderate (5/10)	--	Mild-Moderate (2/10)	37, 34
"	Mild (0.7/8)	Moderate (5.2/8)	Mild (8/110)	23
Alkyl glycidyl ether (C8-C10)	Moderate (3.3/8)	--	Mild (11.7/110)	30

TABLE XIV-5 (CONTINUED)

DEGREE OF IRRITATION* PRODUCED IN RABBITS
BY TOPICAL APPLICATION OF UNDILUTED GLYCIDYL ETHERS

Compound	Skin		Eyes	Reference
	Single Application (24 hr)	Repeated Application (1 hr x 5-7 d)	Single Application	
Alkyl glycidyl ether (C12-C14)	Moderate (3.4/8)	--	Mild	30
Butanediol diglycidyl ether	Moderate (5/10)	--	Moderate (5/10)	32
Resorcinol diglycidyl ether	Moderate (5.0/8)	Severe*** (8.0/8)	Moderate (45/110)	33

*Numerical scores are based on the method described by Draize [43] and by Smyth et al [34]. Maximum severity is indicated by a score of 8 for skin irritation and 110 for eye irritation in the Draize system, and by a score of 10 for both skin and eyes in the method of Smyth et al.
**Severe hyperemia of the cornea, disappearing within 96 hr
***Applied for 7 hr x 7 d

TABLE XIV-6

MUTAGENIC ACTIVITY OF GLYCIDYL ETHERS

Compound	Bacterial			Mammalian			Reference
	Ames Test	Body-Fluid Analysis	Host-Mediated Assay	DNA Repair	Micronucleus Test	Dominant Lethal	
AGE	+(0)*	n.d.**	n.d.	n.d.	n.d.	n.d.	57
BGE	+(-)	n.d.	n.d.	n.d.	n.d.	n.d.	57
"	+(-)	-	-	+	-	+	58
CGE	+(-)	+	-	+	-	-	58
DGE	+(-)	n.d.	n.d.	n.d.	n.d.	n.d.	57
PGE	+(-)	n.d.	n.d.	n.d.	n.d.	-	49
Alkyl glycidyl ether (C12-C14)	-(+)	-	?***	-	-	-	58
Dicyclopentadiene glycidyl ether	+(0)	-	-	-	-	-	58
Diglycidyl ether of substituted glycerine	+(0)	n.d.	n.d.	n.d.	n.d.	n.d.	57
Diphenylol propane diglycidyl ether	-(+)	n.d.	n.d.	n.d.	n.d.	n.d.	57
"	+(+)	-	-	?	-	-	58
Neopentyl glycol diglycidyl ether	+(0)	+	?	+	-	?	58

*Character in paretheses indicates the effect of adding rat liver homogenate to the assay: (+) = increased mutagenic activity; (-) = decreased activity; (0) = no effect.
**n.d. = Compound not tested in this system
***? = Inconclusive or nonsignificant positive results

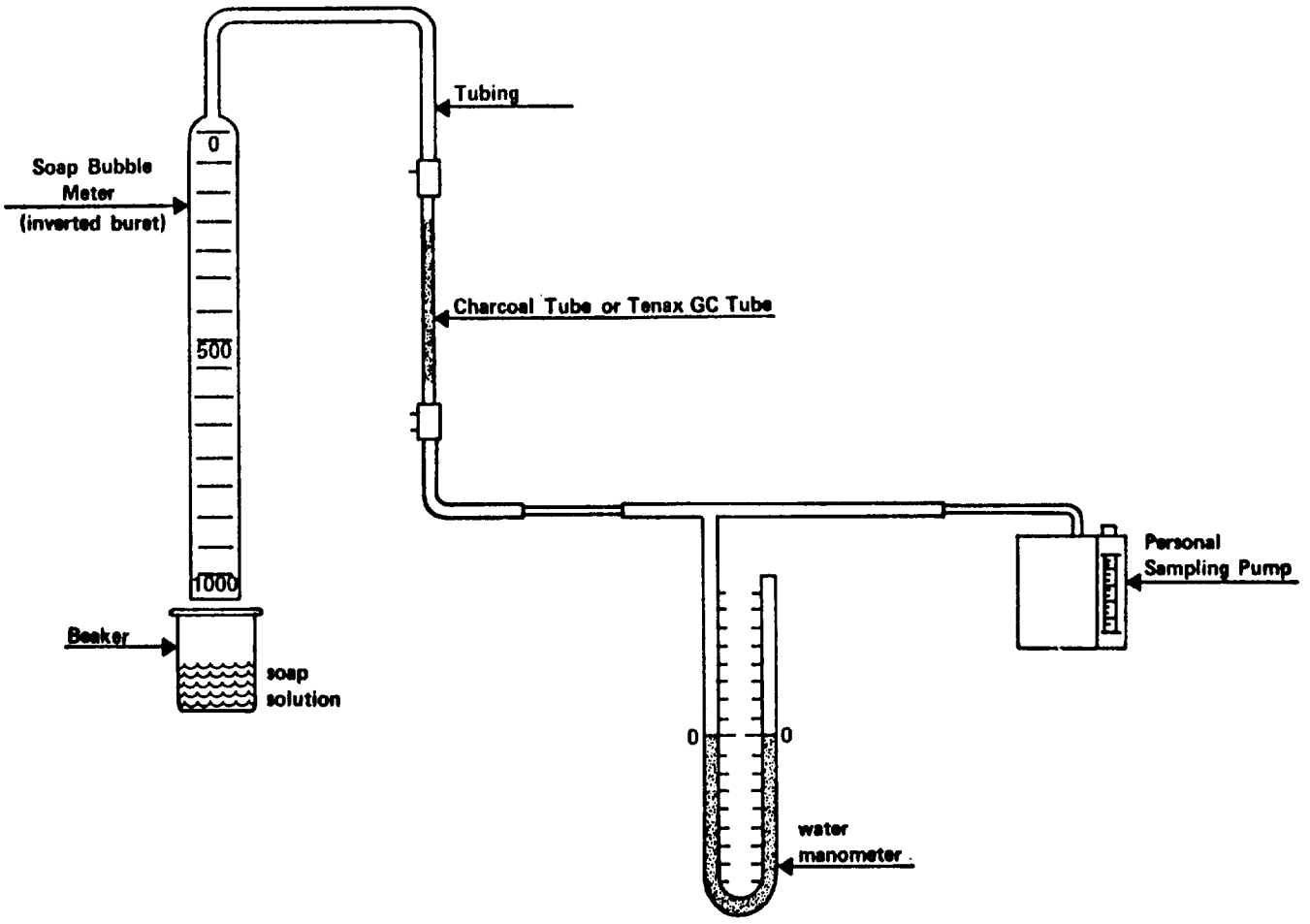

FIGURE XIV-1

CALIBRATION SETUP FOR PERSONAL SAMPLING PUMP
WITH CHARCOAL OR TENAX-GC TUBE

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DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
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