Toxicity of Ethylene Chlorohydrin I: Acute Toxicity Studies

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Abstract □ The LD_{50} of ethylene chlorohydrin was evaluated in mice, rats, rabbits, and guinea pigs, and the range of values was found to fall between 64 and 98 mg./kg. The mean time of death from vapors of the compound was calculated to be 13.3 min. when mice were used as the test animals. Dermal tests in rabbits produced no significant irritant response even when applied undiluted; but when the compound was injected intradermally or instilled into the eye, it was extremely irritating. Ethylene chlorohydrin was found to be cytotoxic in cell culture and to have an inhibitory effect upon cell growth in cultures. Since plastic devices are being ethylene oxide-sterilized and since ethylene chlorohydrin may form as a reaction product, it is necessary to be aware of the toxic potentials of this compound.

Keyphrases □ Ethylene chlorohydrin—acute toxicity studies □ Dermal, intradermal, ocular toxicity—ethylene chlorohydrin □ Inhalation toxicity—ethylene chlorohydrin □ Cell culture growth inhibition—ethylene chlorohydrin

One useful method of sterilizing plastic and elastomeric medical devices is by the use of ethylene oxide alone or in combination with an inert gas. This method of sterilization is now common practice in the medical and paramedical industries which produce nearly an unlimited number of disposable devices for the hospital. Most hospital pharmacies and central supply departments also have installed ethylene oxide units as an adjunct to the autoclave. Small portable units are now appearing in doctors' and dentists' offices.

The presence of residual amounts of ethylene oxide in a polymeric device can present potential toxicologic problems if the ethylene oxide is released to tissue. In recent years, it also has been found that foods and various types of plastic items might contain reaction products of ethylene oxide, namely, ethylene glycol and ethylene chlorohydrin. The latter is formed in the presence of chloride ions, in food or a polymeric material. In 1965, Wesley *et al.* (1) published their results of the production of ethylene chlorohydrin in foods fumigated with ethylene oxide. Two years later, Cunliffe and Wesley (2) brought to the attention of the medical world that ethylene chlorohydrin could result from the sterilization of polyvinyl chloride medical tubings with ethylene oxide. Since then a great deal of interest has developed concerning the potential toxic response from materials sterilized with ethylene oxide.

Ethylene chlorohydrin, also known as 2-chloroethanol and β-chloroethyl alcohol, is a colorless liquid at room temperature, with an odor resembling a mixture of ethyl alcohol and ether[1]. It has a molecular weight of 80.52, a specific gravity of 1.213 (at 20°), and a boiling point of 128.8°. It is miscible in all proportions with water, ethyl alcohol, and ether.

Ethylene chlorohydrin has a number of industrial uses such as solvents for certain types of polymers and lacquers and as a starting material for synthesis of a host of organic compounds. It has been investigated also in agricultural sciences for hastening the early sprouting of dormant potatoes and treating seeds for the inhibition of biological activity (3, 4).

One of the first well-substantiated toxicity observations in humans due to ethylene chlorohydrin was reported by Koelsch in 1927 (5). Of nine cases of chlorohydrin toxicity, two were fatal. Koelsch also conducted animal experiments on the compound. Since then, others (6–9) have presented evidence on the toxicity of ethylene chlorohydrin. Blecket and Strube (10) reported on percutaneous toxicity in humans exposed to chlorohydrin in industrial settings. More recently, Guess (11) presented data on its toxicity to animal tissues and cells in culture.

The formation of ethylene chlorohydrin in polymeric materials due to ethylene oxide sterilization and the possible toxic effects of this compound when released to biological systems prompted this toxicity study of the compound in the hopes of confirming and supplementing existing toxicity data. Since ethylene chlorohydrin is used in the food industry or may be produced in foods containing chlorides when the food is treated with ethylene oxide, the same toxicity information may have further applicability outside the medical and paramedical fields. The results of acute toxicity experiments provide the basis for this report. A subsequent report will describe the results of subacute toxicity studies.

EXPERIMENTAL

Materials—A detailed analysis for purity was not performed on the ethylene chlorohydrin[2] used in these experiments, but gas chromatography revealed the liquid was essentially 99% ethylene chlorohydrin. The liquid was used without further purification throughout the experiments.

LD_{50} Determinations—Experiments were conducted on male mice (Swiss-Webster), male rats (Sprague-Dawley), male and female rabbits (New Zealand albino), and female guinea pigs (Hartley strain). Graded doses of chlorohydrin were administered to groups of four or five animals per dose level, and the animals were observed 1 week for mortalities[3]. The effect of two different routes of administration on the LD_{50} of chlorohydrin was studied in three species of the animals used. The LD_{50} values were then calculated according to Cornfield–Mantel's modification (12) of Karber's method and/or the method of Weil (13).

Dermal administration of chlorohydrin in rabbits was performed by adding the required dose of the compound to a single Webril patch of sufficient size to absorb the agent. The patch was then placed in contact with a nonabraded area of the rabbit's skin (previously clipped of hair) and secured with a polyethylene overwrap. Twenty-four hours later, the bandage was removed, and the rabbit

[1] Ethylene chlorohydrin and chlorohydrin will be used interchangeably throughout this paper.

[2] Obtained from Matheson, Coleman and Bell, East Rutherford, N. J.

[3] Administered as milliliters per kilogram and then converted to milligrams per kilogram.

was observed an additional 6 days for signs of toxicity or mortality. The LD_{50} was calculated on the basis of mortalities that occurred during the 7-day period.

Inhalation Toxicity—Groups of mice were exposed to air–chlorohydrin vapors for periods ranging from 10 to 15 min. The animals that survived the exposure were removed and observed for 7 days for deaths.

The inhalation chamber consisted of an 8.75-l. all-glass desiccator. Filtered air, at a rate of 1 l./min., was bubbled through ethylene chlorohydrin in a glass flask; the resulting air–chlorohydrin mixture was passed into the chamber. Five mice were exposed in the chamber at one time, and the procedure was repeated to give a total of 10 mice for each exposure duration.

It was estimated, by the method of Silver (14), that the concentration of chlorohydrin vapor in the chamber would reach 80% equilibrium with the incoming air vapor in approximately 14.1 min.

Dermal Irritation—Dermal irritation of ethylene chlorohydrin was tested in albino, New Zealand rabbits using a modification of the Draize method (15) and that of Wolven and Levenstein (16). A volume of 0.2 ml. of the test liquid was placed on a 0.5-in. square Webril cotton patch which was then applied to the shaved backs of New Zealand rabbits. The Webril patch was covered by a 1.27- × 2.54-cm. (0.5 × 1-in.) 12-ply cotton gauze, which in turn was covered with a polyethylene sheet of approximately the same dimensions and secured with cellophane tape. Four to six test sites were employed per rabbit, as well as a positive (8% w/v sodium lauryl sulfate in water) and a negative (normal saline) control site. All sites were covered with an unfolded piece of gauze and secured with adhesive tape encircling the torso of the animals. To impede further the volatilization of the test material and to protect the test and control sites, the torso was covered with a film of polyethylene and secured with cellophane tape. The rabbits were placed in individual cages for 24 hr., after which the bandages were removed and the sites of application examined.

Initial trials with the method described indicated that rapid absorption of the compound and the total dose of chlorohydrin employed led to death of the animals within 24 hr.[4]. For this reason the dose was reduced and fewer sites were used in each animal to permit the animal to survive for at least 24–48 hr.

Intradermal Irritation—A volume of 0.2 ml. of the test liquid, as such or diluted with normal saline solution, was injected intradermally on the dorsal surfaces (previously freed of hair) of a group of female albino rabbits (New Zealand strain). Dilutions of chlorohydrin were prepared of 10, 20, 40, and 80% (v/v). Further dilutions were made at increments from 0.625 to 5%. Each animal was injected with two of the test solutions at each of four different sites. Two positive control sites (20% ethyl alcohol) and two negative control sites (normal saline solution) were also included in each rabbit. Fifteen minutes after the last injection, trypan blue solution (1% w/v) was injected into the marginal ear vein at a dose of 1 ml./kg. At 0.5, 1, 5, 10, 15, 45, and 60 min., the sites of injections were examined and scored for irritancy as compared to the control sites. The scoring system used was as follows:

0 = No color (no irritation)—equivalent to saline control
± = Doubtful response
1 = Light-blue coloration (slightly irritating)
2 = Distinct blue coloration throughout (moderately irritating)
3 = Ischemic central area surrounded by deep-blue halo—equivalent to the ethyl alcohol control (markedly irritating)

The highest irritation response regardless of time was used in calculating the average irritant score of each solution but, in most instances, the maximal intensity was observed at the 60-min. period.

Eye Irritation—Solutions of chlorohydrin in normal saline were prepared in concentrations similar to those used for the "intradermal test." A volume of 0.1 ml. of the test solution was instilled into the superior temporal quadrant of the rabbit's right eye, while the left eye served as an untreated control. At least two rabbits were used for each test solution. Each of the rabbit's eyes was examined every 30 min. for 3 hr. following instillation of the test sample, and the response was recorded using the following scoring system:

0 = No irritation—comparable to untreated control eye
± = Doubtful irritation
1 = Definite conjunctiva and palpebral irritation with significant edema
2 = Either iritis or palpebral irritation with significant edema
3 = Eye swollen shut, with or without purulent discharge, and generally accompanied by iritis and corneal damage

The average response for each solution was calculated based upon the highest response observed.

Tissue Culture—*Agar Overlay Method*—Ethylene chlorohydrin, as such, and dilutions in distilled water were tested on monolayers of mouse fibroblasts (L-cells) according to the method of Guess *et al.* (17). A volume of 0.2 ml. of the test solution was pipeted onto a paper disk which was previously placed firmly on the agar[5]. Each Petri dish was kept in an incubator for 24 hr.; it was then removed and the cells under and immediate to the paper disk were examined for a cytotoxic response as indicated by loss of a vital strain (neutral red) which has been added to the cells. The test solutions were prepared in concentrations similar to those used in the "eye test."

Inhibitory Dose, 50% (ID_{50})—A method similar to that of Rosenbluth *et al.* (18) was employed to evaluate the growth-inhibiting effect of chlorohydrin using mouse fibroblast L-cells, strain 929. The medium used for maintenance of stock cultures consisted of modified Basal Medium Eagle (BME)[6] supplemented with 5% newborn calf serum, 1% L-glutamine, and 50 mcg./ml. of streptomycin sulfate. Stock cultures were subcultured every 72 hr.; cells for inoculum were harvested with the aid of 0.05% trypsin in phosphate-buffered saline, the trypsin was removed from the monolayer by aspiration, and the trypsinized cells were resuspended in BME supplemented with 10% calf serum and 2% L-glutamine.

A 2-ml. semiautomatic Cornwall syringe was used to deliver a 1.0-ml. aliquot of cell suspension (2×10^5 cells) into each culture tube. Various concentrations of chlorohydrin, dissolved in BME (no serum or glutamine), were prepared immediately prior to use. These were selected to provide adequate data between 20 and 80% inhibition. One milliliter of the appropriate toxicant–BME solution was added to each tube containing 1 ml. of the cell suspension.

Table I—LD_{50} Values of Ethylene Chlorohydrin

Species	Sex	Route of Administration	Acute Toxicity: LD_{50}, mg./kg.	Acute Toxicity: 95% Confidence Limits
Mice	Male	Intraperitoneal	98.3	71.9–134.6
	Male	Oral	81.4	66.4– 99.7
Rats	Male	Intraperitoneal	64.0	53.7– 76.9
	Male	Oral	71.3	57.8– 88.6
Rabbits	Either sex	Intraperitoneal	84.6	63.7–112.5
	Either sex	Dermal	67.8	41.2–111.7
Guinea pigs	Female	Intraperitoneal	85.8	—[a]

[a] 95% confidence could not be calculated.

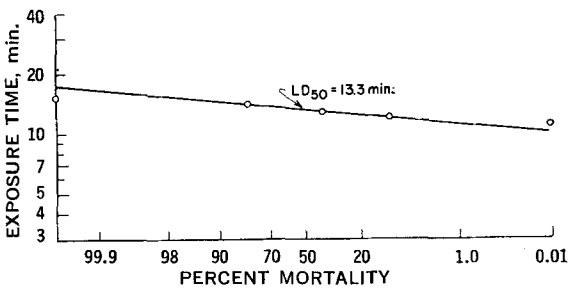

Figure 1—*Inhalation toxicity of ethylene chlorohydrin to mice plotted as exposure time* versus *percent mortality.*

[4] This test was performed before the "dermal toxicity test" leading to the LD_{50} value as described in the previous section.

[5] In this procedure, a thin layer of agar is placed over the surface of the monolayer of cells.

[6] BME was prepared according to Eagle (19, 20), except that magnesium was added as magnesium chloride in a concentration of 177 mg./l.

Controls received identical treatment except for the absence of chlorohydrin.

Both treated and control culture tubes were incubated for 72 hr., and the protein content of each tube was determined by the colorimetric method of Oyama and Eagle (21). Percent growth was calculated using the following expression:

$$\% \text{ growth} = \frac{(A - B)}{(A_0 - B)} \times 100 \qquad \text{(Eq. 1)}$$

where A is the mean absorbance for cultures receiving a specific treatment, A_0 is the mean absorbance for the untreated control cultures, and B is the initial (zero time) mean absorbance of untreated control cultures. Mean absorbance values were obtained from 5 replicate tubes for the treated cultures and 10 replicate tubes for zero-time and 72-hr. untreated control cultures.

RESULTS AND DISCUSSION

Determination of LD_{50}—The LD_{50} values for chlorohydrin in the various species are summarized in Table I and, as indicated, fall into a relatively narrow range. Goldblatt (8) reported an LD_{50} of 72 mg./kg. in rats by the oral route and 56 mg./kg. by the intraperitoneal route, and Johnson (22) found an oral LD_{50} in rats of 77 mg./kg., all of which are comparable to the values reported here.

The routes of administration employed in this study appear to have little influence on the LD_{50} of chlorohydrin (Table I). Dermal absorption of chlorohydrin in the rabbit is rapid and complete as indicated by its lethal activity. Absorption of chlorohydrin through the skin was reported by Goldblatt (8) in mice, by Ambrose (9) and Guess (11) in rabbits, and by Blecket and Strube (10) in man.

Inhalation Toxicity—When the data were analyzed graphically by plotting mortality against duration of exposure (as Bliss probits *versus* log time) (23), a linear relationship was obtained from which it was possible to evaluate the time required to kill 50% of the animals (Fig. 1). This lethal time dose (LT_{50}) was found to be 13.3 min.

As conducted in this study, inhalation toxicity experiments did not permit calculation of an LD_{50} but did permit an approximation of the lethality of the compound based upon the duration of inhalation required to kill 50% (LT_{50}) of the mice. However, the actual concentration of ethylene chlorohydrin in the inhalation chamber was not constant. It increased from zero when the animals were initially placed into the chamber to 80% equilibrium with the air–chlorohydrin mixture after 14 min. The extremely short period of time for death to occur confirms the high degree of toxicity of the compound when inhaled. Ambrose (9) reported concentrations of 7.5 p.p.m. for 1 hr. as being lethal to rats. The threshold limit value (TLV)[7] for chlorohydrin is given as 5 p.p.m.

Intradermal Irritation and Eye Tests—Chlorohydrin, undiluted, produced an intradermal irritation score of 3 (marked irritation), while dilutions equivalent to 1 and 5% (v/v) solutions gave an average score of ± (doubtful) and 1 (slight irritation), respectively.

In the eye test, a value of 3 (highest irritancy) was recorded for the undiluted chlorohydrin; dilutions of chlorohydrin from 20 to 80% also produced a 3 response. On further dilution, in the range of 2.5–10%, an average score of 2 resulted while a 1.25% solution gave a response of 1. Dilutions containing less than 1% chlorohydrin were nonirritating.

Guess (11) reported the responses of the rabbit to ethylene chlorohydrin when it was placed in contact with skin, injected intradermally or intramuscularly, placed on penile tissue, and instilled into the eye. He noted that undiluted ethylene chlorohydrin did not produce any significant irritant response when placed on the surface of the skin. When undiluted ethylene chlorohydrin was injected intradermally or intramuscularly, a very pronounced irritation developed at the sites of the injections. Irritation of the eye was produced by instillation of the undiluted compound. Similar results were observed when the compound was placed on penile mucosa. Irritation and tissue damage were progressively less pronounced as the solutions became more dilute. When the compound was sufficiently diluted, it produced no tissue damage or irritation. In the study by Guess (11), ethyl alcohol was employed as a standard irritant and was compared with the irritant response produced by chlorohydrin. The author noted that the tissue responses to chlorohydrin was much greater than to comparable concentrations of alcohol.

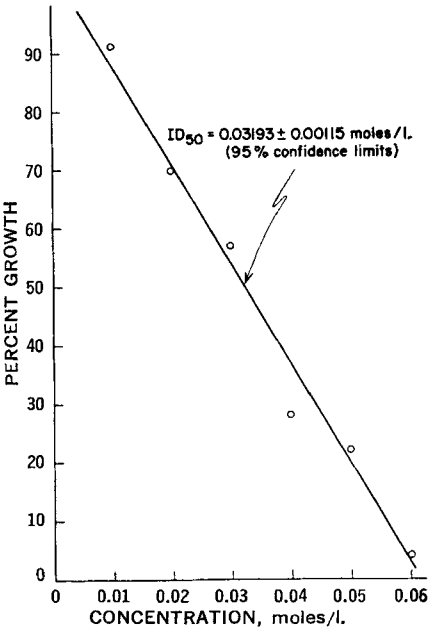

Figure 2—*Growth of L-cells in media containing various concentrations of ethylene chlorohydrin.*

In the current study, no significant irritant response was evident when the compound was applied to the skin of rabbits for 24 or 48 hr. This finding confirms the results of Guess (11). The lack of an irritant response is thought to be due to the rapid absorption of the compound into the systemic circulation, probably at a rate equal to or greater than penetration of chlorohydrin through the epidermis. This rapid passage of the chemical through the skin prevents accumulation of the agent to a critical concentration in dermal tissue. However, when the compound is injected directly into the tissues, a sufficient local concentration is achieved to produce a definite damaging effect. Dilution of the compound to a 5 or 1% solution reduced and abolished the intradermal response. Marked eye irritation with possible corneal damage was noted in this study when the undiluted compound was instilled into the eye. The response persisted even when the concentration of the agent was progressively diluted to 20%. Dilutions below 1.25% failed to produce eye irritation, and intermediate concentrations produced graded degrees of irritation. Guess (11) reported that chlorohydrin failed to cause eye irritation at a 10% concentration.

Tissue Culture—In this test where monolayers of cells were cultured in Petri dishes and covered with a thin layer of agar, the response from a test solution was recorded as an "all or none" response. Chlorohydrin in concentrations of 10–100% was found to be cytotoxic. Dilution to 5% or less abolished the cytotoxic response, A similar test by Guess (11) on chlorohydrin was comparable, except he reported a "noncytotoxic" response at 2% and less.

Cell growth inhibition tests permitted the data to be plotted as percent growth *versus* concentration of chlorohydrin (Fig. 2). By the method of least squares, it was possible to calculate the ID_{50} (inhibitory dose necessary for a 50% reduction in cell growth). The ID_{50} was found to be 0.03193 ± 0.00115 mole/l. ($p = 0.05$) or approximately 2570 mg./l. For comparison, the ID_{50} of ethyl alcohol was found to be 0.155 mole/l. Although it is not valid to compare LD_{50} values in animals with LD_{50} values in cell culture for a number of apparent reasons, it is interesting to note that the toxicity of chlorohydrin in cell culture is approximately 5 times that of ethyl alcohol but approximately 100 times as lethal as alcohol in rats.

According to Johnson (24), the toxic action of ethylene chlorohydrin in rats is due to metabolism of the compound to chloroacetaldehyde in target organs. Cells in tissue culture may not con-

[7] Threshold Limit Values, American Conference of Government Industrial Hygienists, Cincinnati, Ohio (1970). The Royal Institute of Chemistry (1960) placed the maximum allowable concentration (MAC) at 5 p.p.m., Goldblatt and Chiesman (1944) suggested it be 2 p.p.m., while the Merck Index (1960) suggests it should probably be below 1 p.p.m.

vert the chlorohydrin into the more toxic metabolic product, chloroacetaldehyde, or may simply be less sensitive to its effects and therefore can tolerate relatively higher concentrations of ethylene chlorohydrin.

Toxic Liability to Chlorohydrin—The results of the acute toxicity experiments reported here contribute additional evidence that ethylene chlorohydrin can be dangerous to life when inhaled or when the liquid comes in contact with skin. Small amounts of ethylene chlorohydrin falling on the skin may lead to systemic toxicity without showing significant signs of local irritation. If the dermal LD_{50} for rabbits (Table I) could be extrapolated to man, a volume slightly more than a teaspoonful could be lethal to the average (70 kg.) man if it contacts the skin and is not washed off immediately.

Plastic Devices—It is now well established that in the presence of chlorides, ethylene oxide sterilization of plastic medical devices can generate, as one of the reaction products, the highly toxic ethylene chlorohydrin. A potential local and systemic toxic hazard might thus be created if sufficient chlorohydrin or ethylene oxide is present in the device and is released to tissue or biological fluids (25). Proper degassing procedures for a plastic device after ethylene oxide sterilization can generally remove all of the residual ethylene oxide present in the device but this may not be the case for ethylene chlorohydrin (if present). To ensure safety to the patient, all ethylene oxide-sterilized devices should be biologically tested for possible toxic reaction products prior to their release for patient use. In most instances, manufacturers of plastic medical and dental devices are performing toxicity tests on their devices. Unfortunately, in many hospitals this type of testing program is not being conducted when "inhospital" ethylene oxide sterilization is performed on "reusable devices."

REFERENCES

(1) F. Wesley, B. Rourke, and O. Darbishire, *J. Food Sci.*, **30,** 1037(1965).

(2) A. C. Cunliffe and F. Wesley, *Brit. Med. J.*, **May 27, 1967,** 575.

(3) F. E. Denny, *J. Soc. Chem. Ind.*, **47,** 239(1928).

(4) M. Z. Condon, F. R. Andrews, M. G. Lambou, and A. M. Altschul, *Science*, **105,** 525(1947).

(5) F. Koelsch, *Zentralbl. Gewerbehyg. Unfallverhuet.*, **14,** 312 (1927).

(6) E. L. Middleton, *J. Ind. Hyg.*, **12,** 265(1930).

(7) M. W. Goldblatt and W. E. Chiesman, *Brit. J. Ind. Med.*, **1,** 207(1944).

(8) M. W. Goldblatt, *ibid.*, **1,** 213(1944).

(9) A. M. Ambrose, *Arch. Ind. Hyg. Occup. Med.*, **21,** 591(1950).

(10) G. Blecket and G. Strube, *Int. Arch. Gewerbepathol. Gewerbehyg.*, **24,** 45(1968).

(11) W. L. Guess, *Toxicol. Appl. Pharmacol.*, **16,** 382(1970).

(12) J. Cornfield and N. Mantel, *Amer. Stat. Ass. J.*, **45,** 181 (1950).

(13) C. S. Weil, *Biometrics*, **8,** 249(1952).

(14) S. D. Silver, *J. Lab. Clin. Med.*, **31,** 1153(1946).

(15) J. H. Draize, "Dermal Toxicity," in *Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics*, Association of Food and Drug Officials of the United States, Austin, Tex., 1959, pp. 46–49.

(16) A. Wolven and I. Levenstein, *J. Soc. Cosmet. Chem.*, **18,** 199(1967).

(17) W. L. Guess, S. A. Rosenbluth, B. Schmidt, and J. Autian, *J. Pharm. Sci.*, **54,** 1545(1965).

(18) S. A. Rosenbluth, W. L. Guess, and J. Autian, *J. Biomed. Mater. Res.*, **1,** 197(1967).

(19) H. Eagle, *J. Exp. Med.*, **102,** 595(1955).

(20) H. Eagle, *Science*, **122,** 50(1955).

(21) V. I. Oyama and J. Eagle, *Proc. Soc. Exp. Biol. Med.*, **91,** 305(1956).

(22) M. K. Johnson, *Biochem. Pharmacol.*, **14,** 1383(1965).

(23) C. I. Bliss, *Ann. Appl. Biol.*, **22,** 134(1935).

(24) M. K. Johnson, *Biochem. Pharmacol.*, **16,** 185(1967).

(25) C. W. Brunch, "Sterilant Residue in Materials Treated With Gaseous Ethylene Oxide or Propylene Oxide," presented at the Parenteral Drug Association Meeting, New York, N. Y., November 1967.

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Effects of Interaction with Surfactants, Adsorbents, and Other Substances on the Permeation of Chlorpromazine through a Dimethyl Polysiloxane Membrane

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Abstract □ Effects of the nature of two membranes, hydrogen-ion concentration, and some additives on the *in vitro* permeation of chlorpromazine were examined at 37° employing the diffusion technique. Disappearance of chlorpromazine from one compartment of a diffusion cell to the other through a dimethyl polysiloxane membrane appeared to be a partition-controlled process over the pH range 4.1–6.4 and a diffusion-controlled process over the pH range 6.8–7.4. Decreased permeation of the drug in the presence of surfactants and bile salts was attributed to micellar effect and insoluble complex formation. Reduction in permeation in the presence of activated carbon, kaolin, and talc was rationalized on the basis of the adsorption of the drug on solid surfaces. Caffeine, riboflavin, and saccharin also decreased the permeation of the drug; their effect was interpreted to be due to soluble complex formation with the drug. Retarding effects of milk and gastric mucin may be ascribable to protein binding.

Keyphrases □ Chlorpromazine permeation—dimethyl polysiloxane membrane □ Adsorbents, surfactants, interaction with chlorpromazine—membrane permeation effect □ Diffusion cell—chlorpromazine membrane permeation determination

Ingested drugs have to dissolve in gastrointestinal fluids and pass through a succession of membranes before they reach the circulating bloodstream. The physiological availability of drugs will be influenced by, among other factors, how the presence of various substances in the gastrointestinal lumen modifies the