phy," Wiley-Interscience, New York, N.Y., 1971, p. 178.
(7) S. Bergström, R. Ryhage, B. Samuelsson, and J. Sjorvall, *J. Biol.*, **238**, 3555(1963).
(8) L. R. Snyder, *J. Chromatogr. Sci.*, **10**, 200(1972).
(9) R. G. Stehle and T. O. Oesterling, APhA Academy of Pharmaceutical Sciences Abstracts, APhA Academy of Pharmaceutical Sciences, Washington, DC 20037, 1973, p. 62.

ACKNOWLEDGMENTS AND ADDRESSES

Received June 28, 1973, from *The Upjohn Company, Kalamazoo, MI 49001*

Accepted for publication January 24, 1974.

The technical assistance of Mr. Scott Douglas is greatly appreciated.

Effects of γ-Irradiation on 2-Chloroethanol Formation in Ethylene Oxide-Sterilized Polyvinyl Chloride

S. BOGDANSKY ˣ and P. JEFFERY LEHN

Abstract □ γ-Irradiation prior to sterilization with ethylene oxide is shown to enhance 2-chloroethanol formation in a surgical, hospital grade, polyvinyl chloride tubing. The site of formation and the insignificantly low 2-chloroethanol levels produced in this manner are discussed.

Keyphrases □ Ethylene oxide, use as sterilant of polyvinyl chloride—effects of γ-irradiation on 2-chloroethanol formation □ 2-Chloroethanol—effects of γ-irradiation on formation in ethylene oxide-sterilized polyvinyl chloride □ Irradiation, gamma—effects on 2-chloroethanol formation in ethylene oxide-sterilized polyvinyl chloride □ Polyvinyl chloride, ethylene oxide sterilized—effects of γ-irradiation on formation of 2-chloroethanol

When the formation of 2-chloroethanol from the ethylene oxide resterilization of previously γ-irradiated polyvinyl chloride was first reported (1), no data were presented and none have been reported supporting this observation, although references to these findings have been made (2, 3). This study was undertaken because of the lack of definitive data on the effects of γ-irradiation on 2-chloroethanol formation in polyvinyl chloride and the growing concern over the biological impact of this residue in sterilized polyvinyl chloride medical devices.

EXPERIMENTAL

Materials—Surgical, hospital grade, polyvinyl chloride tubing was used[1].

Procedure—The tubing was cut into samples approximately 1 cm long, weighing 120 ± 3 mg. The samples were divided into four groups and placed in glassine envelopes. One group received 2.5 Mrads of γ-irradiation from a ^{60}Co source and one received 5.0 Mrads. The two irradiated groups and one nonirradiated group were then exposed to a 1099-mg/liter concentration of ethylene oxide (12/88, ethylene oxide/freon 12 mixture) for 4.5 hr. A temperature of 55° and relative humidity of 50 ± 5% were maintained under a sterilization pressure of 15 psig. The fourth group remained as the untreated control. Immediately following sterilization with ethylene oxide, samples for 2-chloroethanol analysis from each group were placed in glass vials with rubber septa and crimped metal caps and extracted in 5 ml distilled water for 48 hr at 72°. The same number of treated samples were also extracted after 2 and 4 days of ambient aeration.

Additional samples from the group that was only sterilized with ethylene oxide were placed in vials for ethylene oxide analysis, extracted, and analyzed by the head-space technique (4). These samples were extracted at the same time as the 2-chloroethanol samples to compare the concentrations of both residues.

A separate group of samples was soaked in 2-chloroethanol[2] for 2.5 hr and heated for 3.5 hr at 72°. This material was sampled every 2–3 days over a 28-day ambient aeration period to assess 2-chloroethanol desorption.

Apparatus—Analysis of 2-chloroethanol was accomplished using a published GLC method (5) with slight modifications.

A gas chromatograph[3], equipped with a hydrogen flame-ionization detector connected to a 1-mv strip-chart recorder[4], was employed.

A U-shaped glass column, 1.83 m (6 ft) × 0.20 cm (0.078 in.) i.d., was packed with 3% polyethylene glycol[5] coated on a styrene–divinylbenzene copolymer resin[6] (80–100 mesh, less than 50 m^2/g surface area). The column was prepared according to the method used by Spitz and Weinberger (5) for their Column B.

The column was initially conditioned for 24 hr at 200° with a nitrogen flow rate of 30 ml/min. The column was then connected to the detector, and 2.5-μl injections of distilled water were made approximately every 15 min for several hours at a column temperature of 180°.

The instrument was operated isothermally at a column temperature of 170°, an injector temperature of 195°, and a detector tem-

Table I—Concentration of 2-Chloroethanol and Ethylene Oxide as a Function of Aeration Time (Mean ± *SD*)

Aeration, days	2-Chloroethanol, ppm: Ethylene Oxide Sterilized Only[a]	2-Chloroethanol, ppm: 2.5 Mrads + Ethylene Oxide Sterilized	2-Chloroethanol, ppm: 5.0 Mrads + Ethylene Oxide Sterilized	Ethylene[a] Oxide, ppm: Ethylene Oxide Sterilized Only
0	35 ± 2	329 ± 5	354 ± 7	8954 ± 438
2	n.d.[b]	19 ± 1	21 ± 1	33 ± 2
4	n.d.	n.d.	n.d.	n.d.

[a] Samples from the same ethylene oxide sterilization cycle were analyzed for both residues. [b] Not detected: detection limit 10 ppm.

[1] Tygon, S-50-HL, 4.762 mm (0.1875 in.) o.d. × 3.175 mm (0.125 in.) i.d., Norton Plastics and Synthetics Division, Akron, Ohio.

[2] Baker grade (anhydrous), J. T. Baker Chemical Co.
[3] Varian model 2100.
[4] Varian model 20.
[5] Carbowax 20M, Union Carbide Corp.
[6] Chromosorb 101, Johns-Manville Products Corp.

Table II—Levels of 2-Chloroethanol in Soaked Samples

Aeration, days	2-Chloroethanol, ppm	Aeration, days	2-Chloroethanol, ppm
0	44,132	14	569
3	17,747	17	235
5	9,825	19	159
7	4,866	21	91
10	2,442	28	65
12	1,364	—	—

perature of 220°. Nitrogen was used as the carrier gas with a flow rate of 30 ml/min. The hydrogen flame was maintained with an air flow of 350 ml/min and a hydrogen flow of 40 ml/min. The strip-chart recorder was operated at a speed of 50.8 cm (20 in.)/hr.

Standards, prepared by dissolving 2-chloroethanol by weight in distilled water, contained 515 (0.51), 87 (0.08), 44 (0.04), and 8.8 ppm (0.008 μg/μl) 2-chloroethanol. The linearity of the response of the detector to 2-chloroethanol concentration was established. All calculations were based on peak height comparisons between 3-μl injections of the unknowns and appropriate standards.

RESULTS AND DISCUSSION

Table I shows that polyvinyl chloride samples that were γ-irradiated, ethylene oxide sterilized, and not aerated produced about 350 ppm of 2-chloroethanol. Contrary to previous findings (1), about 35 ppm of this residue was found in samples that were only ethylene oxide sterilized; this was presumably due to small amounts of free chloride in the polymer. Although there seems to be an increase in 2-chloroethanol formation in samples that received 5.0 Mrads as compared to 2.5 Mrads, the difference is small and is not considered meaningful. Table I also shows the corresponding 2-chloroethanol concentrations for each aeration period.

While the effect of preirradiation is clear, the question of where the 2-chloroethanol is formed remains open. As discussed previously (3), it is possible that 2-chloroethanol is formed during the water extraction by the reaction of ethylene oxide with chloride generated during ^{60}Co sterilization[7]. The elevated temperature of the extraction could accelerate such a reaction. The data in Table I support this hypothesis; as the concentration of ethylene oxide decreases, the concentration of 2-chloroethanol also decreases. Alternatively, as pointed out previously (3), 2-chloroethanol might be formed in the polymer during gas sterilization by the reaction of ethylene oxide and polyvinyl chloride and may desorb during sample aeration. This would account for the drop in 2-chloroethanol as a function of aeration time (Table I). To test this hypothesis, 2-chloroethanol was incorporated into polyvinyl chloride tubing by a soaking technique and its desorption from the polymer was followed. Table II shows that 2-chloroethanol desorbs from this polyvinyl chloride at concentrations comparable to those present in the doubly sterilized samples (*i.e.*, between 325 and 360 ppm). However, this relatively slow rate of desorption is insufficient to account for the large decrease in 2-chloroethanol concentration observed for the doubly sterilized samples. This decrease seems to suggest that desorption is not a significant factor and that 2-chloroethanol is probably formed during the extraction, although some formation during sterilization is also possible.

[7] For discussion of the effects of irradiation in polyvinyl chloride, see R. Salovey, in "The Radiation Chemistry of Macromolecules," vol. II, M. Dole, Ed., Academic, New York, N.Y., 1973, p. 37.

CONCLUSIONS

While the data show that irradiation prior to ethylene oxide sterilization produces 350 ppm of 2-chloroethanol in unaerated, surgical, hospital grade, polyvinyl chloride tubing, published toxicology data have shown this relatively low level to be nonirritating and nontoxic. McDonald *et al.* (6) found the maximum nontoxic concentrations to be 10,000 ppm for topical application and 5000 ppm for intraocular application in rabbits. In a study to assess the extent and nature of tissue damage elicited by 2-chloroethanol, Bruckner and Guess (2) concluded that concentrations of 50,000 ppm or less when injected intracutaneously in rabbits did not produce cellular damage or necrosis. Guess (7) found no damage to cells in culture at levels of 20,000 ppm and no intradermal irritation in rabbits at 10,000 ppm. Unpublished data[8] showed levels up to 100,000 ppm to be nonirritating to rats when introduced *via* subcutaneous polyvinyl chloride implants.

REFERENCES

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

(2) J. V. Bruckner and W. L. Guess, *Toxicol. Appl. Pharmacol.*, **22**, 29(1972).

(3) J. E. Whitbourne, J. A. Mogenhan, and R. R. Ernst, *J. Pharm. Sci.*, **58**, 1024(1969).

(4) S. Romano, J. Renner, and P. Leitner, *Anal. Chem.*, **45**, 2327(1973).

(5) H. D. Spitz and J. Weinberger, *J. Pharm. Sci.*, **60**, 271(1971).

(6) T. O. McDonald, M. D. Roberts, and A. R. Borgmann, *Toxicol. Appl. Pharmacol.*, **21**, 143(1972).

(7) W. L. Guess, *ibid.*, **16**, 382(1970).

ACKNOWLEDGMENTS AND ADDRESSES

Received October 23, 1973, from the *Ethicon Research Foundation, Somerville, NJ 08876*

Accepted for publication January 17, 1974.

[x] To whom inquiries should be directed.

[8] Toxicology Section, Ethicon Research Foundation.