

The fractional volume compression *versus* applied pressure plots up to the first linear region of the relative density *versus* pressure plots were used to calculate the coefficients of the Cooper-Eaton equation (Table V). Figure 6 gives the fractional volume compression *versus* pressure plots of the granulation made with hydroxypropyl methylcellulose and dried to different moisture contents. The experimental data were fitted to the results of the calculations using Eq. 4. The values of the coefficients were obtained from the best-fit curves.

The larger values of the dimensionless coefficient a_1 compared to a_2 (Table V) suggest that a large percentage of compression was achieved by filling large holes. The sum of coefficients a_1 and a_2 ranged from 0.97 to 1.01, indicating that compression is achieved by the two probabilistic processes of filling large and small holes by rearrangement, fragmentation, and plastic flow.

The coefficient k_1 gives the pressure needed to fill the large holes. This process occurs primarily by particles sliding past one another, which may require elastic deformation or even slight fracturing or plastic flow of particles. This process occurs at low pressures and is reflected in small k_1 values (Table V).

The coefficient k_2 indicates the pressure needed to fill small voids that are substantially smaller than the original particles. These voids can be filled by plastic flow or by fragmentation. This process requires high pressure, which is reflected in large k_2 values (Table V). Thus, k_2 provides more information about granulation compressibility since, during the rearrangement process, granules do not produce hard compacts. The k_2 values given in Table V indicate that, at lower moisture contents, methylcellulose- and povidone-containing granules are more compressible than granules made with the other binders. At higher moisture contents, methylcellulose-containing granules are more compressible than granules made with other binders. The k_2 values also suggest that the higher moisture-containing granules are more compressible than those of lower moisture content. This finding is in complete agreement with the C_1 values of the Heckel plots (Table IV), which suggest that the high moisture granules compress more easily than the low moisture ones.

The tablet crushing strength *versus* pressure profiles of granulations made with the selected binders containing different moisture contents are given in Figs. 7-9. At lower moisture contents (0.75-1.12%), methyl-

cellulose-containing tablets gave higher crushing strengths than those made with granules containing other binders. The tablets made from granules without a binder were lower in crushing strength than the tablets made from granules containing binders.

At higher moisture levels (1.95-2.44%), differences in tablet crushing strength due to the binders were small (Fig. 8). Povidone-containing granules were better in crushing strength only at high pressure. Granules without a binder showed lower tablet crushing strengths compared to those with different binders.

Figure 9 compares the tablet crushing strength *versus* pressure profiles of the tablets compressed from granulations made with hydroxypropyl methylcellulose at different moisture levels. These results clearly show that the lower moisture-containing granules gave a higher crushing strength compared to the higher moisture-containing granules and that these differences became more pronounced as pressure was increased.

At higher moisture levels, it is important to consider the moisture-induced crushing strength increase phenomenon (6). Table VI gives the initial crushing strength and the crushing strength after a 24-hr exposure to ambient room conditions of tablets compressed at a given pressure. The crushing strength of tablets containing povidone, methylcellulose, and hydroxypropyl methylcellulose increased after overnight exposure to ambient room conditions. Pregelatinized starch-containing tablets did not show any change in crushing strength after overnight exposure to ambient room conditions. In the absence of a binder, the tablet crushing strength actually decreased after overnight exposure to ambient room conditions.

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Leaching of 2-(2-Hydroxyethylmercapto)benzothiazole into Contents of Disposable Syringes

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Abstract □ A contaminant was found to leach into the contents of two brands of disposable syringes. It was identified as 2-(2-hydroxyethylmercapto)benzothiazole and is believed to be formed during manufacture of the syringes as a result of a reaction between 2-mercaptobenzothiazole, a rubber vulcanization accelerator, and ethylene oxide, used for sterilization. The contaminant was isolated from the rubber plunger-seal and identified using mass, NMR, and UV spectroscopic methods. The amount of contaminant appearing in the contents of syringes was measured; up to 140 µg was found under clinically relevant conditions. This finding has

important implications with respect to the use of these syringes for drug administration and for the collection of blood for drug analyses.

Keyphrases □ 2-(2-Hydroxyethylmercapto)benzothiazole—leaching into contents of disposable syringes, isolation, identification, and quantitation □ Syringes, disposable—leaching of 2-(2-hydroxyethylmercapto)benzothiazole, isolation, identification, and quantitation □ Contaminants—2-(2-hydroxyethylmercapto)benzothiazole, leaching from disposable syringes

Several previous reports described the problems associated with the leaching of compounds from plastic infusion bags and giving sets and from blood collection tubes. The measurement of drug levels in blood and plasma samples for toxicological, therapeutic monitoring, or

pharmacokinetic purposes may be hampered by such contaminants. In addition, the accumulation of plasticizers in patients' organs after transfusion of blood from plastic storage bags was reported (1).

Recently, contamination of blood collected in evacuated

tubes¹ with a compound identified as tris(2-butoxyethyl)-phosphate was reported (2). Leaching of this compound into blood causes a decrease in plasma protein binding and redistribution to the red blood cells of several drugs including propranolol (3), imipramine (4), alprenolol (4), quinidine (5), and lidocaine (6). Consequently, the measured plasma concentrations of these drugs were spuriously low. Tris(2-butoxyethyl) phosphate, leached into blood samples from collection tubes, interfered directly with the analysis of postmortem specimens (2) and with GLC analysis of theophylline (7). Another plasticizer, di(2-ethylhexyl) phthalate, also was reported to interfere with a GLC assay for disopyramide (8).

During recent work involving the development of a high-performance liquid chromatographic (HPLC) assay for blood and plasma corticosteroids (9), a large chromatographic peak interfered with the assay. The absence of the interfering compound in samples collected directly into a glass container indicated that it originated in the collection system and was not due to endogenous material or contamination of the reagents used in extraction. The compound originated in the disposable syringes used for blood collection.

The identification of the source of the compound, its isolation, and the elucidation of its chemical structure are reported here.

EXPERIMENTAL

Identification of Contaminant Source—Three brands of disposable plastic syringes (A², B³, and C⁴) were used. Initially, one syringe of each brand (10–12-ml capacity) was filled through a 19-gauge needle⁵ with freshly distilled water (10 ml) and allowed to stand for 2 min. Another sample of water (10 ml) was allowed to stand for 2 min in a blood storage tube containing ammonium heparin (100 U/10 ml) and separation granules⁶. From each of these sources 1 ml (10%) of the water was extracted with methylene chloride⁷, which was then concentrated at 45° and chromatographed as described previously for plasma samples (9). The reversed-phase HPLC column⁸, with a mobile phase of methanol-water (60:40) at a flow rate of 1.25 ml/min, was coupled to a UV detector set at 254 nm. An aliquot (1 ml) of distilled water, which had been measured directly into a glass extraction tube, was also analyzed as already described.

To pinpoint the source of contamination, this procedure was repeated with three Brand A syringes, three Brand C syringes, and three samples of water measured into glass extraction tubes. In addition, the barrels of three Brand A syringes with the plungers removed and needles crimped were each filled with 10 ml of distilled water, and three rubber plunger-seals from Brand A syringes were removed and immersed in beakers containing 10 ml of distilled water. The syringes and components were in contact with the water for 2 min, and 1 ml was assayed.

To establish that the contaminant was extracted from the syringes into blood as well as into water and to confirm that the chromatographic peak observed in plasma samples was not an endogenous compound, the following experiment was performed. Blood was drawn from a single subject through a cannula⁹ and three-way tap¹⁰ using the three brands of syringes in turn. The total blood volume (15 ml) was drawn within 3 min. The blood was transferred to three heparinized plastic tubes for centrifugation; in each case, 1 ml of the resulting plasma was assayed.

Identification of Contaminant—To facilitate identification of the compound of interest, several syringes of each brand were allowed to stand, containing water, for 10 min. The water was subsequently ex-

tracted, the concentrated extract was chromatographed, and the fraction of the HPLC eluate corresponding to the peak of interest was collected. The fractions from each brand of syringe were pooled separately and evaporated to dryness in a 45° water bath under a nitrogen stream. The residues were dissolved in 1 ml of distilled water and extracted with methylene chloride. The extracts then were concentrated. To provide sufficient sample for NMR studies, derivatization procedures, and UV spectroscopy, ~500 µg of the contaminant was collected by pooling the HPLC fractions from 20 Brand A syringes (35-ml capacity) as already described.

GLC-mass spectrometric analyses were carried out on a chemical-ionization mass spectrometer¹¹ interfaced to a gas chromatograph¹². The glass GLC column (0.91-m × 2 mm i.d.) was packed with a phenyl methyl silicone phase¹³ and was programmed from 150 to 200° at 10°/min. Injection port and interface temperatures were maintained at 260°. Methane chemical-ionization mass spectra were generated by using methane as both the GLC carrier and chemical-ionization reactant gas. A flow rate of 20 ml/min generated an ion source pressure of 130 Pa. Deuterium oxide chemical-ionization mass spectra were generated by introducing deuterium oxide into the methane plasma *via* a variable leak (10). Ammonia chemical-ionization mass spectra were obtained by using helium as the GLC carrier gas at a flow rate of 20 ml/min and adding ammonia through a makeup T piece at the end of the column. The ammonia flow rate was adjusted to give an ion source pressure of 130 Pa. The electron beam energy for chemical ionization was 110 eV, and the ion source and analyzer regions of the mass spectrometer were operated at 60–100°. An interactive data system¹⁴ was used for data acquisition and processing.

High-resolution electron-impact mass spectra were obtained¹⁵ using the direct insertion probe inlet and an electron beam energy of 70 eV.

Derivatization reactions were carried out by dividing a methylene chloride extract from Brand A syringes into two portions and evaporating each to dryness. One portion was treated with 10 µl of a silylation reagent¹⁶ by heating at 50° for 1 hr. The other portion was treated with excess freshly distilled ethereal diazomethane for 15 min at room temperature and then evaporated to a volume of <50 µl in a water bath at 40°.

2-(2-Hydroxyethylmercapto)benzothiazole (II) was synthesized from 2-mercaptobenzothiazole (I) and 2-chloroethanol according to the method of Sexton (11). The product, recrystallized twice from benzene, had a melting point of 56–57° [lit. (11) 56–58°].

Quantitation of Contaminant—Once the compound leaching from the syringes had been identified and synthesized, the recrystallized product was used as a standard to measure how much contaminant was leached from syringes under several sets of conditions. Brand A syringes were used for all three parts of this experiment.

1. Several syringes (2 and 10 ml) were filled with various volumes of distilled water and allowed to stand for 5 min before an aliquot was injected directly onto the HPLC column.

2. Seven syringes (20 ml) were each filled with 10 ml of distilled water and allowed to stand for 4–300 min before an aliquot was injected onto the column.

3. The effect of two different vehicles that are used for parenteral dosage forms was examined. A pediatric formulation, which consisted of 25 µg of digoxin/ml of propylene glycol (40%)–alcohol (10.5%)–water¹⁷, was studied because the contaminant displayed lipophilic tendencies in its solvent extraction and HPLC characteristics and, therefore, was expected to partition more favorably into a less polar solvent than water and because the presence of the contaminant may have one of its most serious implications in infant therapy. Water (1 ml) was drawn into each of three 2-ml syringes and allowed to stand for 2, 5, or 12.5 min, and the digoxin formulation (1 ml) was drawn into each of four 2-ml syringes and allowed to stand for 1, 2, 5, or 11 min. Aliquots were injected directly into the chromatograph, and an injection also was made of the digoxin dosage form, which had not been in contact with the plastic syringes.

RESULTS

Source of Contaminant—The interfering peak observed when developing an HPLC assay for plasma samples had a retention time of 6.5

¹ Vacutainer, Becton-Dickinson, Rutherford, N.J.

² Monoject, Sherwood Medical Industries, Deland, Fla.

³ Terumo, Terumo Aust. Pty. Ltd., Melbourne, Australia.

⁴ Pharma-Plast, A.H.S./Aust. Pty. Ltd., Balgowlah, Australia.

⁵ Monoject brand.

⁶ Disposable Products Pty. Ltd., Sydney, Australia.

⁷ GR grade, Merck, Darmstadt, West Germany.

⁸ RP-8, Brownlee, Santa Clara, Calif.

⁹ Dwellcath, Tuta Laboratories, Sydney, Australia.

¹⁰ Pharma-Plast brand.

¹¹ Model 3200, Finnigan Corp., Sunnyvale, Calif.

¹² Model 9500, Finnigan Corp., Sunnyvale, Calif.

¹³ Three percent OV-17 on Chromosorb W AW DMCS, 120–140 mesh, Applied Science Laboratories, State College, Pa.

¹⁴ Model 6110, Finnigan Corp., Sunnyvale, Calif.

¹⁵ AEI MS-9 mass spectrometer, Kratos Ltd., Manchester, England.

¹⁶ TRI-SIL, Pierce Chemical Co., Rockford, Ill.

¹⁷ Lanoxin pediatric injection, Wellcome Australasia, Rosebery, Australia.

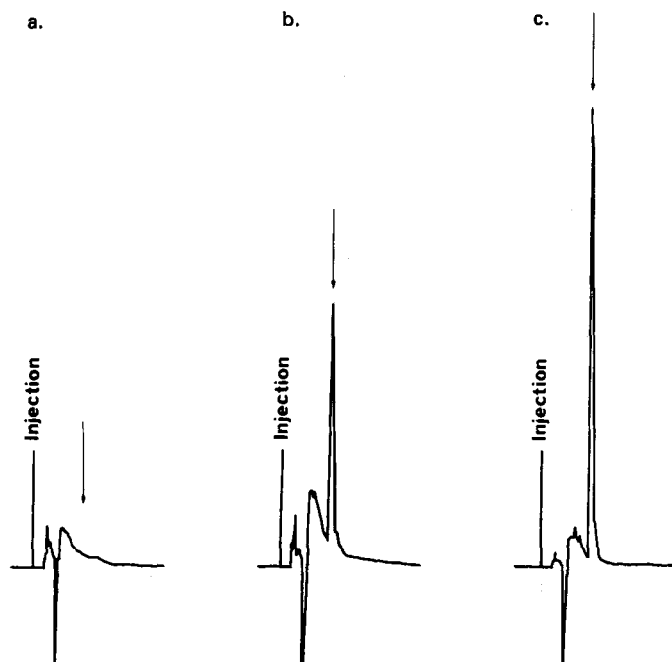


Figure 1—HPLC traces of extracts of distilled water that had been standing in Brand C (sensitivity 0.05 a.u.s) (a), Brand B (0.02 a.u.s) (b), and Brand A (0.05 a.u.s) (c) syringes. The arrow marks retention time of 6.5 min.

min under the chromatographic conditions described previously (9). When water was allowed to stand in the syringes and blood storage tubes for 2 min and aliquots were analyzed, a large chromatographic peak was again observed at 6.5 min in the extracts of the water from Brands A and B syringes. Extracts of the water from the blood storage tube and the Brand C syringe had chromatograms identical to that of the extract of the water that had been measured directly into the glass extraction tube.

Figure 1 illustrates the magnitude of the interfering peak observed when 10% of the water in the A–C syringes was extracted and chromatographed. Brand B syringes released less of the compound chromatographing at 6.5 min than did the A syringes. Later studies in which all of the water in the syringe was extracted showed that the A and B syringes also released into the water compounds that chromatographed with retention times of 3.8 and 4.7 min but with peak heights ~5% that of the peak at 6.5 min. These peaks were not seen in extracts of water from the C syringe.

In turn, plasma (1 ml) harvested from blood collected into the three brands of syringes was extracted and chromatographed. No peak was observed at 6.5 min when a C syringe had been used to collect the blood, but large peaks were seen in the extracts of plasma collected in A and B syringes.

The results of the experiment in which various parts of the Brand A syringe were allowed to contact the water are summarized in Table I. Although these results were semiquantitative, the severalfold differences in the heights of the peaks indicated that the contaminant was probably being leached from the rubber seal on the plunger. The average height of the peak resulting from only the syringe barrel contacting the water was <10% of the height of the peak resulting from the intact syringe being filled with water. In contrast, the peak resulting from extraction of water in which the plunger-seal had been immersed was three times greater than the peak from the intact syringe.

Identification of Contaminant—GLC–mass spectral analysis of the fraction collected from HPLC after extraction of the contents of Brand A syringes revealed a single GLC peak with a retention time of 2.2 min. The presence of a molecular ion at m/z 211 in the electron-impact mass spectrum of this GLC peak and a protonated molecular ion (MH^+) at m/z 212, together with methane adduct ions at m/z 240 ($M + C_2H_6^+$) and 252 ($M + C_3H_8^+$) in the methane chemical-ionization mass spectrum (Fig. 2), suggested a molecular weight of 211. Confirmation was obtained from the ammonia chemical ionization mass spectrum, which contained a single ion peak at m/z 212. The observation of a MH^+ ion in the ammonia spectrum indicated that the compound was a stronger gas phase base than ammonia (12).

The relative abundances of the isotopic ion peaks at m/z 212, 213, and

Table I—Height ^a of the Contaminant Peak after 2 Min of Contact between Water and Brand A Syringe Components

	Intact Syringe	Barrel Only	Plunger-Seal
	404	34	875
	384	37	1250
	416	28	1500
Mean	401	33	1208
Relative percent	100	8.2	301

^a All peak heights measured in millimeters and normalized to 0.01 a.u.s.

214 in the ammonia chemical-ionization mass spectrum, measured accurately using the selected ion monitoring mode, were 100, 11.81, and 9.40 (average of five measurements), respectively, which indicated the empirical formula $C_9H_9NOS_2$ (calculated isotopic abundances: 100, 11.91, and 9.44, respectively). This result was confirmed by high-resolution electron-impact mass spectrometry (measured mass 211.0128, calculated for $C_9H_9NOS_2$ 211.0125). The deuterium oxide chemical-ionization mass spectrum contained a quasimolecular ion at m/z 214. However, ionization of the molecule by addition of a D^+ ion would be expected to give an ion at m/z 213. Therefore, the observation of m/z 214 in the spectrum showed that the molecule contains one exchangeable hydrogen atom (13). The appearance of an ion peak at m/z 194 in both the methane (Fig. 2b) and deuterium oxide chemical-ionization mass spectra ($MH^+ - H_2O$ and $MD^+ - D_2O$, respectively) indicated the presence of a hydroxyl group, which would account for the exchangeable hydrogen atom.

Treatment of the compound with the silylation reagent and analysis by GLC–mass spectrometry showed a single product with a molecular weight of 283, corresponding to a monotrimethylsilylated derivative. The compound, however, failed to react with diazomethane and, therefore, must be an aliphatic alcohol rather than a phenol or carboxylic acid.

The base peak in the electron impact mass spectrum (Fig. 2a) was at m/z 167, and the relative abundances of the isotope peaks at m/z 168 and 169 indicated that this ion still contained the two sulfur atoms. In many respects, the spectrum below m/z 170 resembled that of I. The relative abundances of the ions at m/z 166, 140, 123, 108, 91, 69, and 45 in the spectrum of the compound were quite similar to those reported for I (14).

On the basis of the mass spectral data, II was indicated. Although the major fragment ions in both the electron-impact and chemical-ionization mass spectra could be rationalized in terms of this structure (Schemes I and II), other isomers in which the side chain was attached to the phenyl ring could not be excluded. However, these isomers can be excluded on the basis of NMR spectroscopic data.

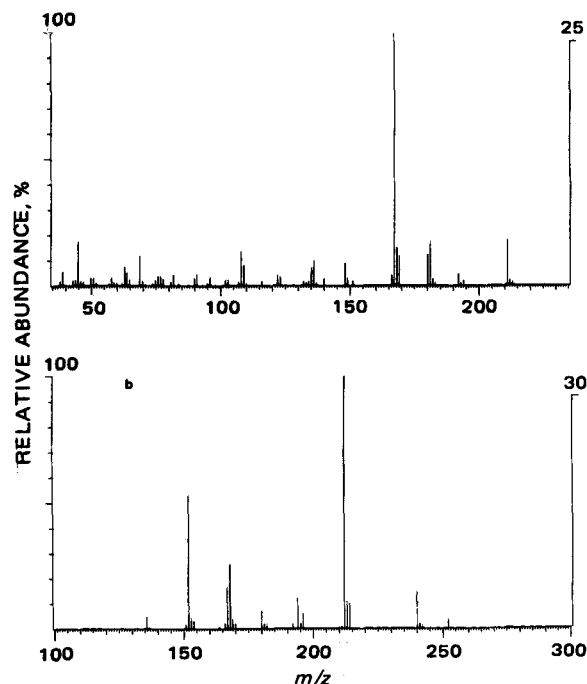
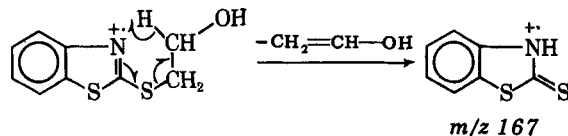
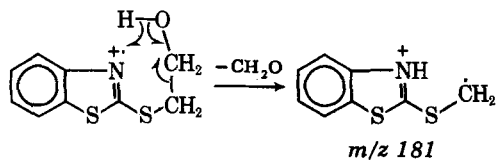
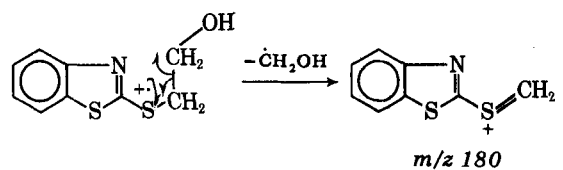
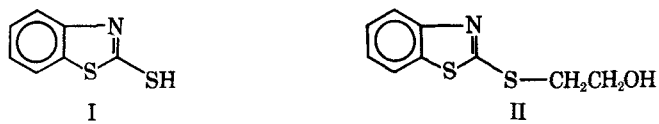


Figure 2—Mass spectra of the contaminant identified as 2-(2-hydroxyethylmercapto)benzothiazole (II). Key: a, electron impact; and b, methane chemical ionization.



Scheme I—Electron-impact-induced fragmentation of II.

The NMR spectrum (recorded at 58°) contained signals at δ 7.15–7.85 (m, 4H, aromatic CH), 3.94 (m, 2H, CH₂–O–), 3.45 (t, 2H, CH₂–S–), and 3.03 (t, 1H, OH, removed by exchange in D₂O). Significantly, no signal could be attributed to a C-2 proton. In the NMR spectrum of benzothiazole, this signal occurred as a sharp singlet at δ 8.95. Moreover, the splitting pattern of the four aromatic protons in the spectrum of the compound extracted from syringes was very similar to that observed for the four protons on the phenyl ring of benzothiazole. Therefore, it was concluded that the side chain must be attached to C-2 of the benzothiazole ring as shown in II. In keeping with this structure, irradiation at δ 3.03 caused the signal at δ 3.94 to change to a triplet, and irradiation at δ 3.94 caused the signal at δ 3.45 to collapse to a singlet.

This structure was also supported by UV spectrophotometric data in that the observed absorption maxima ($\lambda_{\max}$) at 224 and 279 nm were almost identical to the maxima reported for 2-(methylmercapto)benzothiazole ($\lambda_{\max}$ 224 and 280 nm) (15).

As final proof, 2-(2-hydroxyethylmercapto)benzothiazole (II) was synthesized using the method of Sexton (11). The mass, NMR, UV, and IR spectra and chromatographic retention times (GLC and HPLC) of the authentic compound were identical to those of the compound extracted from the Brand A syringes. The mass spectra (electron-impact and chemical ionization) and GLC and HPLC retention times of the compound extracted from the A and B syringes were identical; therefore, it was concluded that both brands released II into their contents.

Table II—Amount of 2-(2-Hydroxyethylmercapto)benzothiazole (II) in Various Volumes of Water Allowed to Stand in Brand A Syringes for 5 Min

2-ml Syringe			10-ml Syringe		
Volume, ml	$\mu\text{g/ml}$	μg	Volume, ml	$\mu\text{g/ml}$	μg
0.5	3.78	1.89	2.0	3.59	7.18
1.0	1.57	1.57	5.0	1.65	8.26
2.0	0.98	1.97	10.0	0.89	8.87

Table III—Amount of 2-(2-Hydroxyethylmercapto)benzothiazole (II) Leached with Time into Water (10 ml) from 20-ml Brand A Syringes *

Minute	II, μg
4	13.8
9	16.1
30	34.0
60	53.2
150	93.0
240	108.7
300	139.5

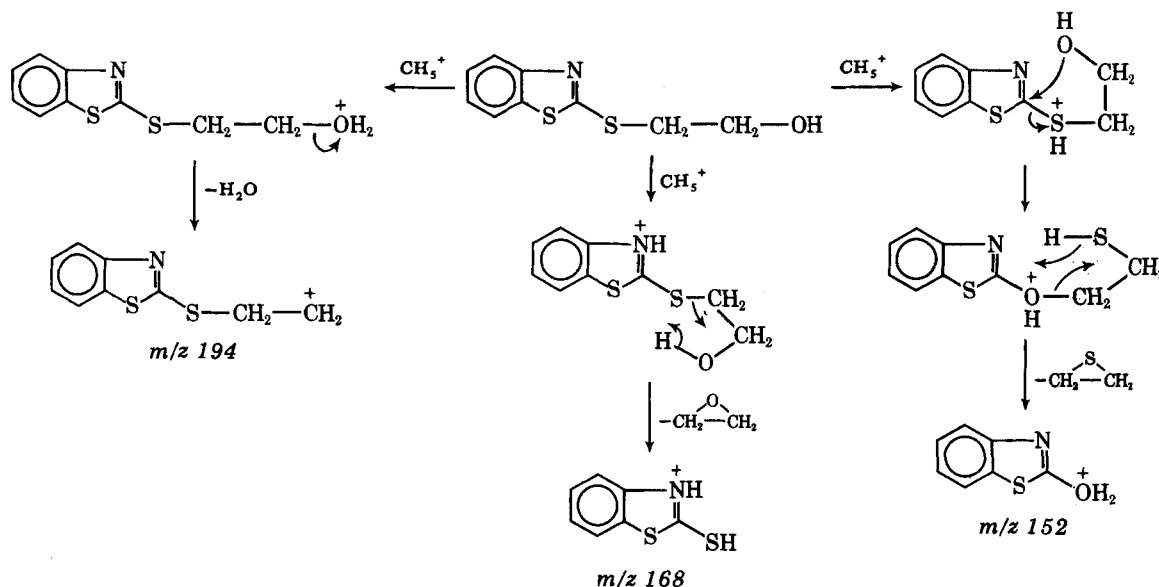
* Each data point represents analysis of water from a different syringe.

Quantitation of II—The amount of II found in the contents of the syringe after 5 min was similar for a given syringe capacity regardless of the volume of water in the barrel (Table II). As may be expected, the 10-ml syringes, with a greater surface area of rubber exposed to the liquid, released more II (mean 8.1 μg) than the 2-ml syringes (mean 1.8 μg). In a 20-ml syringe, the amount of II in the water increased as the contact time between the rubber and water increased, even up to 5 hr when 140 μg was found (Table III). Compound II moved quickly into the water from the rubber, as was shown by the presence of several micrograms of II in the syringe contents after only 4–5 min (Tables II and III). Table IV shows the amounts of II that leached into 1 ml of water and 1 ml of the digoxin formulation after various times. The results were very similar for the two solvents and followed the trends established in the previous experiments.

These data (Tables III and IV) suggest that the appearance of II in the syringe contents is not limited by the extent of its solubility in the solvent, but it is more likely to be restricted by the rate at which it can move out of the rubber matrix.

DISCUSSION

The early experiments, designed to identify the source of the contaminant, indicated that II was coming from the rubber seal on the plunger of Brands A and B syringes. This finding was consistent with their structure since both brands have soft rubber seals while Brand C does not. Compound II is not commonly used in rubber manufacture, but



Scheme II—Methane chemical-ionization-induced fragmentation of II.

Table IV—Amount of 2-(2-Hydroxyethylmercapto)-benzothiazole (II) in the Contents of 2-ml Brand A Syringes Containing Different Solvents

Distilled Water, 1 ml		Digoxin Formulation, 1 ml	
Minute	II, μ g	Minute	II, μ g
2	1.25	1	1.05
5	1.95	2	1.31
12.5	3.34	5	2.83
		11	3.26

it has been reported to be a reaction product of I, a widely used vulcanization accelerator, and ethylene oxide (16), used in this case for sterilization of the syringes. A sample of I had the same HPLC retention time (4.7 min) as the later of the two smaller peaks found in the chromatograms of extracts from A and B syringes, supporting the view that II is formed from I.

Rubbers formulated with I were reported to present stability problems when subjected to γ -radiation (17), so syringes containing I in rubber components are likely to be sterilized with ethylene oxide. One brand of syringe that has a rubber plunger-seal and is sterilized by ethylene oxide¹⁸ did not leach I and II into water. This brand has been reported as nontoxic to amniotic fluid cell cultures whereas other brands have been associated with cultures that fail to thrive (18, 19).

More information is available on the toxicity of I than on that of II. Compound I was identified as one of the allergens responsible for allergies to the rubber in clothing and shoes (20) and also was reported to be mutagenic in fruit flies (21) and embryotoxic in rats (22). The toxicity of I and II was studied in cell lines and in mice by Guess and O'Leary (16). Using a suggested standard of toxicity rating, they reported that both compounds would be rated as highly toxic in mice when given by the parenteral route and moderately toxic when ingested. They also suggested that care should be exercised if these compounds could gain access to the systemic circulation and reported that II was more toxic than I when administered parenterally or orally.

While II was first noticed because of its appearance in blood samples, its transfer from the rubber seal to solutions administered parenterally must be considered. Although no toxicity data are reported for II in humans, the introduction of microgram quantities of even a moderately toxic foreign compound into the body should be recognized and, if possible, avoided. The results indicate that the amount of II leaching into the syringe contents increases with the time of exposure to the rubber and with the capacity of the syringe, but it is essentially independent of the volume of liquid in the syringe. When 10 ml of water was allowed to remain in a 20-ml syringe for 5 hr, 140 μ g of II was measured in the contents. This may be a cause for concern with obstetric and surgical patients undergoing epidural anesthesia since additional anesthetic solution is often left in a disposable syringe until further pain relief is required several hours later. When such relief is required, the solution containing accumulated II is injected into the epidural space, in close proximity to the cerebrospinal fluid. Compound II may also accumulate in patients who receive several injections while in the hospital or in patients who are on chronic parenteral medication, e.g., diabetics.

The inadvertent administration of II may be of particular importance in hospitalized infants, especially premature infants, children, and patients with impaired elimination. Total parenteral nutrition for infants in some intensive care nurseries is administered from a disposable syringe (10 ml), which may have been filled several hours previously in the aseptic supply area. In this situation, relatively large amounts of II may be administered intravenously.

Brand A syringes were reported previously as the source of a contaminant that interfered in chromatographic assays for chlorpheniramine (23) and oxazepam (24). In this laboratory, II was first noticed as a large chromatographic peak that interfered with plasma steroid assays (9), making accurate measurement of plasma hydrocortisone and beta-methasone levels impossible. Such interference results in a considerable waste of time and materials until the source of the contaminant is identified and a more suitable brand of syringe is used. Moreover, such interference may be present but not recognized if the contaminant co-chromatographs with a drug, resulting in an overestimate of drug con-

centration (24). This situation clearly has the potential to compromise the conclusions drawn from pharmacokinetic and therapeutic monitoring data, with possible implications for clinical management. Alteration of plasma protein binding and distribution between blood components of some drugs has been caused by the contamination of blood samples (25). This more subtle effect has serious implications since it results in spuriously low plasma drug level measurements. The possibility that II could interfere in a similar way must also be considered when blood is collected in disposable syringes.

The presence of contaminants may be overlooked if the compounds do not possess characteristics that cause them to interfere with assays in general use. There may be several other compounds leaching out of syringes, closures, blood collection tubes, and other plastic and rubber apparatus which have not yet been recognized but may have similar implications toxicologically and analytically.

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ACKNOWLEDGMENTS

The authors thank Jacki Winyard for skilled technical assistance and Marion Pozniak and Yvonne Molloy for typing this manuscript.

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