

RESIDUE REVIEWS

VOLUME 55



RESIDUE REVIEWS

Residues of Pesticides and Other
Contaminants in the Total Environment

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Preface

That residues of pesticide and other contaminants in the total environment are of concern to everyone everywhere is attested by the reception accorded previous volumes of "Residue Reviews" and by the gratifying enthusiasm, sincerity, and efforts shown by all the individuals from whom manuscripts have been solicited. Despite much propaganda to the contrary, there can never be any serious question that pest-control chemicals and food-additive chemicals are essential to adequate food production, manufacture, marketing, and storage, yet without continuing surveillance and intelligent control some of those that persist in our foodstuffs could at times conceivably endanger the public health. Ensuring safety-in-use of these many chemicals is a dynamic challenge, for established ones are continually being displaced by newly developed ones more acceptable to food technologists, pharmacologists, toxicologists, and changing pest-control requirements in progressive food-producing economies.

These matters are of genuine concern to increasing numbers of governmental agencies and legislative bodies around the world, for some of these chemicals have resulted in a few mishaps from improper use. Adequate safety-in-use evaluations of any of these chemicals persisting into our foodstuffs are not simple matters, and they incorporate the considered judgments of many individuals highly trained in a variety of complex biological, chemical, food technological, medical, pharmacological, and toxicological disciplines.

It is hoped that "Residue Reviews" will continue to serve as an integrating factor both in focusing attention upon those many residue matters requiring further attention and in collating for variously trained readers present knowledge in specific important areas of residue and related endeavors involved with other chemical contaminants in the total environment. The contents of this and previous volumes of "Residue Reviews" illustrate these objectives. Since manuscripts are published in the order in which they are received in final form, it may seem that some important aspects of residue analytical chemistry, biochemistry, human and animal medicine, legislation, pharmacology, physiology, regulation, and toxicology are being neglected; to the contrary, these apparent omissions are recognized, and some pertinent manuscripts are in preparation. However, the field is so large and the interests in it are so varied that the editors and the Advisory Board earnestly solicit suggestions of topics and authors to help make this international book-series even more useful and informative.

"Residue Reviews" attempts to provide concise, critical reviews of timely advances, philosophy, and significant areas of accomplished or needed endeavor in the total field of residues of these and other foreign chemicals in any segment of the environment. These reviews are either general or specific, but properly they may lie in the domains of analytical chemistry and its methodology, biochemistry, human and animal medicine, legislation, pharmacology, physiology, regulation, and toxicology; certain affairs in the realm of food technology concerned specifically with pesticide and other food-additive problems are also appropriate subject matter. The justification for the preparation of any review for this book-series is that it deals with some aspect of the many real problems arising from the presence of any "foreign" chemicals in our surroundings. Thus, manuscripts may encompass those matters, in any country, which are involved in allowing pesticide and other plant-protecting chemicals to be used safely in producing, storing, and shipping crops. Added plant or animal pest-control chemicals or their metabolites that may persist into meat and other edible animal products (milk and milk products, eggs, etc.) are also residues and are within this scope. The so-called food additives (substances deliberately added to foods for flavor, odor, appearance, etc., as well as those inadvertently added during manufacture, packaging, distribution, storage, etc.) are also considered suitable review material. In addition, contaminant chemicals added in any manner to air, water, soil or plant or animal life are within this purview and these objectives.

Manuscripts are normally contributed by invitation but suggested topics are welcome. Preliminary communication with the editors is necessary before volunteered reviews are submitted in manuscript form.

Department of Entomology
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August 7, 1975

F.A.G.
J.D.G.

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Automation in the pesticide analytical laboratory

By

DANIEL E. OTT*

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I. Introduction

Hundreds of thousands of samples are routinely analyzed for pesticide residues annually in the United States alone. The result has been an acute shortage of analytical personnel adequately trained in this exacting area (GUNTHER 1962). One solution which was suggested (GUNTHER and OTT 1966 a and b) to help alleviate this problem was to automate the major and basic routine residue screening methods to the point where less well-trained personnel can operate the required instrumentation. The available skilled analysts can then be partially freed to devote more of their time to those incisive analytical efforts always associated with aberrant samples and also to the ever-increasing evaluative residue programs required under current legislative restrictions imposed to maintain quality in our air, food, fiber, and water supplies. For example, the problem of establishing realistic values of "acceptable daily intakes" for man for pesticide residues and food additives, often necessitating total diet studies which involve residue investigation of large numbers of samples, has been reviewed by Lu (1973) of the *World Health Organization*; these values must be established for each presently used and each new pesticide chemical "to protect the health of the consumer and to facilitate international trade" (Lu 1973). The inherent advantages of reliability, reproducibility, and speed of an automated analytical system are, therefore, essential to the successful production of adequate numbers of routine analyses in the escalating number of international residue surveillance programs.

The potential for quantitatively determining some pesticide residues automatically was presented by WINTER (1960 b). GUNTHER (1962)

revived interest in the possibilities available and WINTER and FERRARI (1964), followed by discussions by GUNTHER and OTT (1966 a and b), stimulated further interest in this approach to pesticide residue analysis. The approach included emphasis primarily for the use of the automated analytical systems in pesticide residue screening programs. Screening, for the purposes of discussions here, has been defined elsewhere by GUNTHER and OTT (1966 a and b) as "procedures to demonstrate the presence or tolerance-realistic 'absence' of [a pesticide or] groups or categories of pesticides."

GUNTHER and OTT (1966 a and b) espoused the potential definitive usefulness of automated screening for organohalogen, -phosphorus, -sulfur, and -nitrogen compounds in addition to unoxidized-oxidized organophosphorus pesticide chemical activity against cholinesterase (ChE). All these screening techniques have not yet been developed; however, efforts directed toward these goals are discussed below along with several other practical examples of automated pesticide analytical systems. Some systems potentially usable in pesticide analytical laboratories are also discussed.

II. Automated analytical systems for major groups of pesticides

a) Anticholinesterase analyzers

OTT and GUNTHER (1966 a; see also MULLA *et al.* 1966) determined technical grade parathion residues in waterplants by an automated anticholinesterase (anti-ChE) method. This method, based upon the *Technicon AutoAnalyzer*^{®1} method of WINTER (1960 b), was further explored to include techniques for the rapid screening for other anti-ChE insecticides in some other substrates: broccoli, cauliflower, canned peaches, Valencia orange rind, and the skin and pulp of white potatoes (OTT and GUNTHER 1966 b) (see Fig. 1² for the automated system). Techniques for automated determination of anti-ChE organophosphorus compounds adsorbed on thin-layer chromatography (TLC) plate "scrapings" were described by OTT and GUNTHER (1966 c) (Fig. 2).

The AutoAnalyzer for determination of anti-ChE insecticides was examined and modified by other workers in the pesticide residue field; systems were described requiring acetylthiocholine instead of acetylcholine as enzyme substrate (VOSS 1966, VOSS and GEISSBÜHLER 1967, ABOUDONIA and MENZEL 1967, LEEGWATER and VAN GEND 1968, OTT 1968 a).

¹ *Technicon Instruments Corporation, Tarrytown, NY 10591.*

² Note that in this and subsequent figures, all details necessary to operate the systems shown cannot be included; the reader is referred to each original work. Selection of figures for this review is intended to give the reader an idea of the types of modules available and how they may be used and, in many cases, to illustrate basic techniques which may have a wide range of applicability to automated analytical systems.

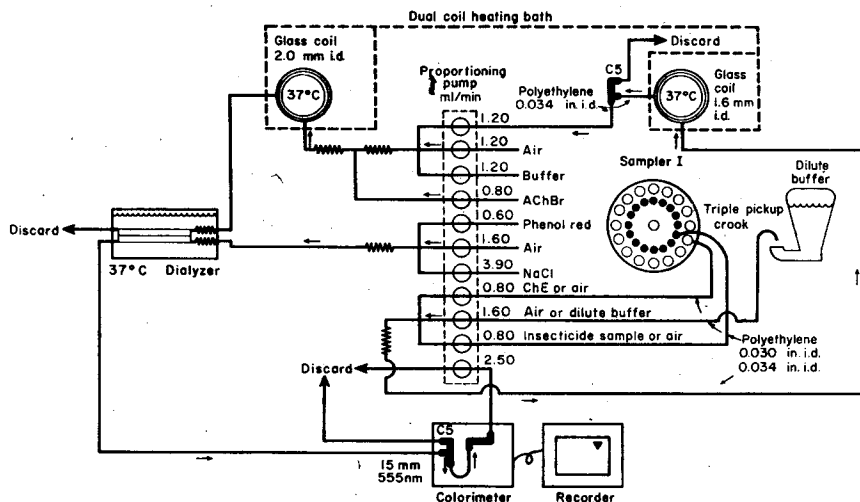


Fig. 1. Automated system for ChE inhibition properties; AChBr = acetylcholine bromide solution (redrawn from OTT and GUNTHER 1966 b).

The four different laboratories represented by these reports apparently independently developed the same basic analyzer system. Methods based upon the same chemistry had earlier been independently reported by HUMISTON and WRIGHT (1965 and 1967) and LEVINE *et al.* (1966) for the automated determination of serum pseudo-ChE and erythrocyte acetyl-ChE (true ChE). The method of VOSS and GEISSBÜHLER (1967) was improved by VOSS (1968) who introduced peacock plasma as a ChE source, which is approximately ten times more sensitive than human plasma ChE to some insecticidal carbamates including carbaryl. For comparison, ZWIG and ARCHER (1958) found human plasma, bovine erythrocyte, horse plasma, and housefly head ChE's in order of increasing sensitivity to be suitable for the manual enzymatic determination of carbaryl residues. Peacock plasma used again in an automated method was also further discussed by VOSS (1969), who determined monocrotophos, for example, down to $0.02 \mu\text{g/ml}$ in aqueous solution, whereas the limit was $0.1 \mu\text{g/ml}$ with human plasma ChE. Quail serum had been used with the advantage of being the most sensitive for organophosphates of all ChE sources tested by LEEGWATER and VAN GEND (1968) for their automated screening method for certain organophosphorus insecticide residues in uncleaned manually-prepared lettuce extract solutions including simple exchange to an aqueous phase. DDVP and mevinphos were respectively and separately detected in fortified lettuce down to 0.02 and 0.5 ppm.

The methods of VOSS (1966) and of ABOU-DONIA and MENZEL (1967)

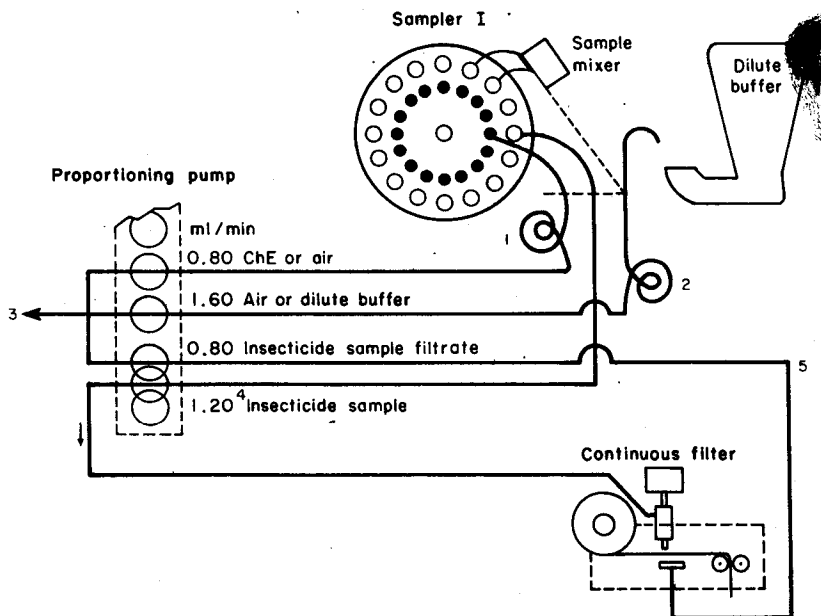


Fig. 2. Flow diagram, of additions and changes to Figure 1, for an automated filtration-analysis system for determining anti-ChE organophosphorus compounds adsorbed on TLC adsorbents; 1 = polyethylene tubing added to delay and time properly addition of ChE solution, 2 = transmission tubing added to delay and time properly introduction of dilute buffer solution, 3 = connection to rest of automated system which from this point is the same as that in Figure 1, 4 = pump tubing with ends cut as short as possible and connected at both ends with lengths of 0.030 in. id polyethylene tubings, also as short as possible, and 5 = same polyethylene tubing used for regular sample pickup line in Figure 1 (redrawn from OTT and GUNTHER 1966 c).

were similar in that they did not use the *Technicon* dialyzer module (Figs. 1 and 3) which requires considerably more periodic maintenance than most other *Technicon* modules. LEEGWATER and VAN GEND (1968) and OTT (1968 a) (Fig. 3) used the dialyzer; OTT (1968 b) found that background responses from several control crop extractives were significantly higher without it.

In retrospect, a few features of the original WINTER (1960 b) method and of the first methods used by OTT and GUNTHER (1966 a and b) may have been desirable and later overlooked. For example, enzyme source in those methods was metered in only with sample (see Fig. 1); thus, inhibition of nonsample-mixed-enzyme by a relatively nonpolar inhibitor compound adsorbed onto and later desorbed from pump tubing essentially could not occur and consequently could not show up on the chart

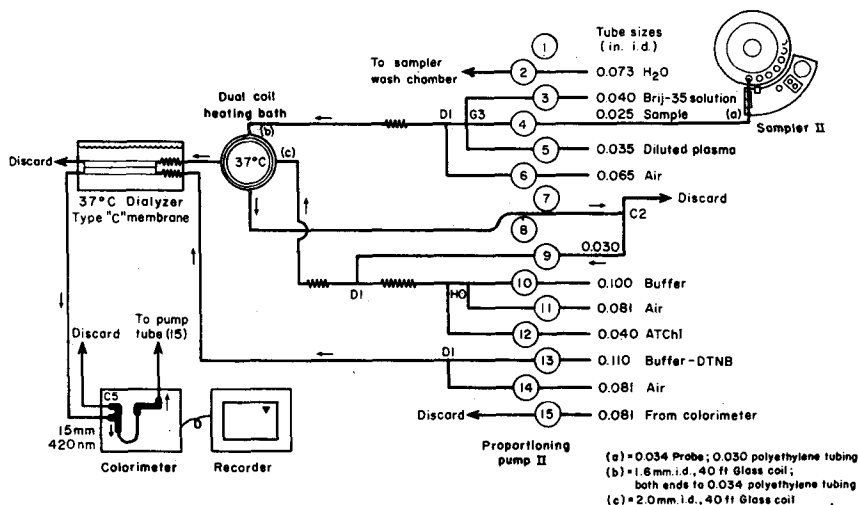


Fig. 3. Automated system which requires acetylthiocholine as substrate for the enzymatic determination of anti-ChE pesticides; ATChI = acetylthiocholine iodide solution and DTNB = 5,5'-dithiodi(2-nitrobenzoic acid) (redrawn from OTT 1968 a).

record as a tailing effect. The controlled introduction of sometimes expensive enzyme solution also aided in its conservation. Furthermore, 30% ethanol was used as a wash for the sample pump tube between samples. Note that the wash was well separated before and after introduction by air as a result of the manner of sampling with sampler I; this separation feature effectively isolated the enzyme from contact with the relatively high concentration of ethanol, valuable as an aid to reduce carry-over effects from one sample to the next.

OTT (1968 a) has discussed one minor possible advantage of tailing vs. nontailing peaks. When analyzing unknown samples a tailing peak indicated that paraoxon or some other relatively nonpolar inhibitor was present in the sample and a nontailing peak indicated that a relatively polar inhibitor such as phosphamidon was present in the sample. This differentiation thus provided some specificity to the method.

Voss (1973) developed a manual technique of microsyringe injection of sample downstream of pump tubings for essential elimination of carry-over effects in his earlier method (Voss 1969). When automated as with an automatic syringe injector device, this concept could be a major contribution to automated analysis.

While the work of ABOU-DONIA and MENZEL (1967) was primarily to develop an automated system for assay of fish brain acetylcholinesterase (AChE), they enlarged the analyzer to demonstrate that it could deter-

Table I. *Inhibition of fish brain AChE by carbamate insecticides (ABOU-DONIA and MENZEL 1967).*

Compound	Molar conc. for 50% inhibition (I_{50})
Hercules 5727 or Union Carbide 10854	4.9×10^{-8}
MesuroI	7.1×10^{-7}
Pyrolan	8.9×10^{-7}
Zectran	1.8×10^{-6}
Mitacil	3.9×10^{-6}
Carbaryl	3.9×10^{-6}

mine anti-ChE pesticides by using fish brain AChE as the enzyme source. Six carbamate pesticides were used and individual concentrations of the carbamates which caused 50% inhibition (I_{50} values) were determined (Table I). These data were compared with I_{50} values previously reported in the literature from manual method determinations in which housefly-head AChE was used. It was concluded that fish brain AChE was, in general, as active for determining these compounds; for Hercules 5727,³ MesuroI® (mercaptodimethur), and Zectran fish brain AChE was more active, and especially so for Zectran.

Some of the AChE sources and other techniques (e.g., fluorescence assay) examined by GUILBAULT *et al.* (1970) in manual anti-ChE methods might well be incorporated into automated methods. For example, fire-ant AChE was specifically inhibited by DDVP and methyl parathion; parathion had little effect on this enzyme, while paraoxon, carbaryl, and various chlorinated pesticides did not inhibit it at all. AChE from two types of houseflies (NAIDM and DDT-resistant strains) were specific for DDVP and carbaryl, while the other pesticides tested had little or no effect up to concentrations of 10^{-6} M. Although not as sensitive as other AChE sources, the sugar boll weevil was totally specific for DDVP below 10^{-6} M concentration; parathion inhibited at concentrations greater than 10^{-6} M and, although paraoxon was not tried, it was expected to inhibit at that concentration. German cockroach AChE was the most sensitive AChE tested for the determination of DDVP, paraoxon, parathion, and methyl parathion, but was the least specific; it was also inhibited by several chlorinated insecticides and herbicides and by carbaryl.

The enzymatic assay of pesticides was a topic given considerable coverage by GUILBAULT (1970) in a review of enzymic methods of analysis. A few of the automated methods listed above were cited; automated methods for studying enzyme reactions and for analyzing enzymes, particularly in the clinical laboratory, were more fully covered. Automated instrumentation and methods for reaction-rate measurements were reviewed by MALMSTADT *et al.* (1972 a and b) in larger reviews of reaction-rate methods.

³ Pesticide and other chemicals mentioned in text are identified in Table III.

As a related topic it is interesting to note that the pseudo-ChE levels in plasma samples taken from a young man during treatment for acute parathion poisoning were monitored by means of the Automatic Clinical Analyzer⁴ as reported by KRAMER (1972). Also, an almost exact duplicate of the ChE AutoAnalyzer reported by LEVINE *et al.* (1966) was used by FOWLER and MCKENZIE (1967) for the detection of mild poisoning of experimental animals by organophosphorus and carbamate pesticides. The ChE AutoAnalyzer developed by WINTER (1960 a) was only slightly modified by SERRONE *et al.* (1966) to permit the continuous determination of whole-blood ChE from femoral vein catheterized monkeys; ChE levels were thus monitored following oral administration of parathion. Another continuous monitoring system for blood ChE from human volunteers by way of intravenous catheter was reported by GROFF *et al.* (1967). This system (Fig. 4) monitored plasma, erythrocyte, and whole blood ChE activities independently and simultaneously by selective use of specific substrates in two of the three channels; each channel is an automated adaptation of the HESTRIN method (1949). The method of WINTER (1960 a) was modified (Fig. 5) by GAGE and LITCHFIELD (1967) to lower the minimum detectability of ChE so that no more than 0.02 ml of human plasma or of erythrocytes was required as samples. Fish plasma ChE was determined by HUNT (1971) with an AutoAnalyzer patterned after the one developed by LEVINE *et al.* (1966). BOUTIN and BRODEUR (1969 and 1970) developed an AutoAnalyzer method (Fig. 6) which determined the three main genetic variants of human serum cholinesterases. The method depended upon the enzymatic hydrolysis of acetylcholine in a bicarbonate buffer from which carbon dioxide was liberated due to the production of acetic acid. Carbon dioxide liberation was determined quantitatively by monitoring the color change (pH change) in a buffer/phenolphthalein solution.

The basic idea of the combination of TLC and automatic analysis, briefly referred to earlier, was put to practical use by VOSS and GEISS-BÜHLER (1967). They presented enolphosphate residue thin-layer "chromatograms," as recorded by an anti-ChE AutoAnalyzer, from eluates of successive uniform scraped zones from developed TLC plates. This combination technique provides specificity which allows determining multiple residues in one extract, after the TLC separation, which is impossible to do with the analyzer alone. The entire method permitted lower limits of detectability of between 0.05 and 0.1 ppm for phosphamidon and monocrotophos and between 0.02 and 0.05 ppm for dicrotophos from various fruits and vegetables. Recoveries were above 80%.

Automated anti-ChE analytical methods were reviewed by GARDNER (1972) within a larger review of enzyme inhibition methods used in pesti-

⁴ E. I. Du Pont de Nemours Co., Inc., Instruments Products Division, Wilmington, Del. 19898.

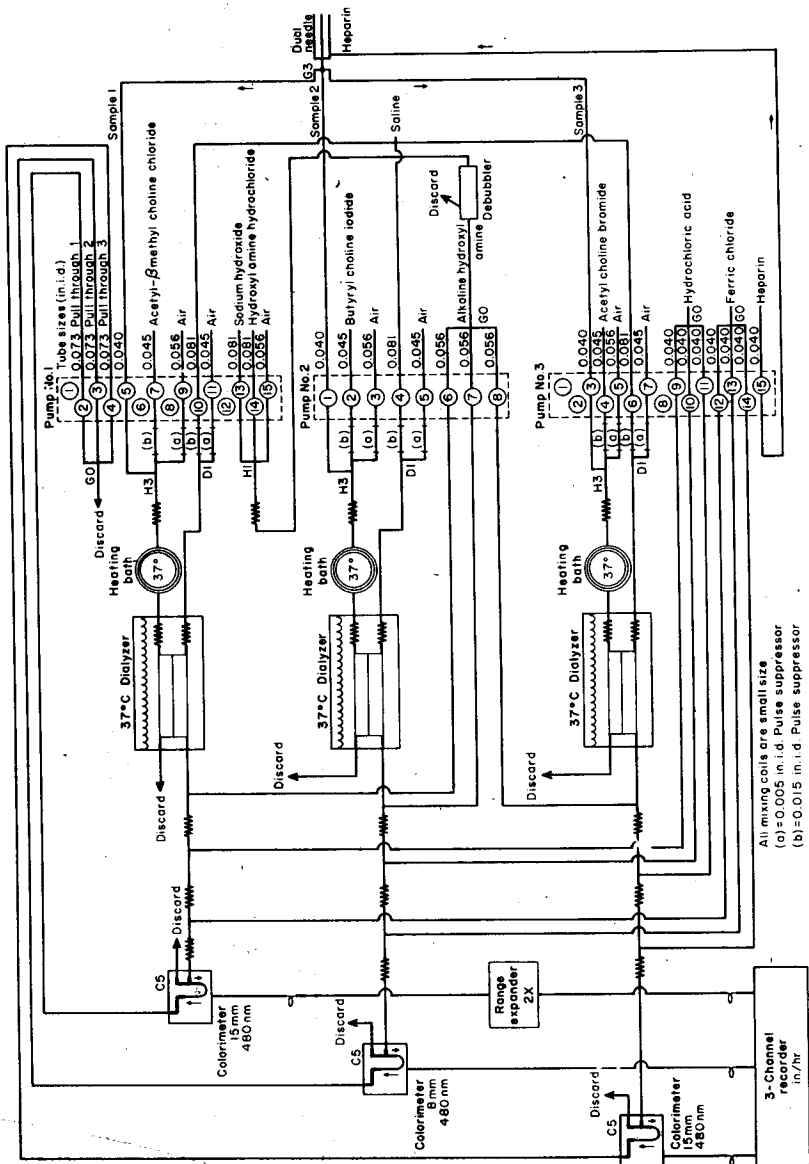


Fig. 4. Automated ChE system for continuous monitoring of blood from human volunteers (redrawn from GROFF *et al.* 1967).

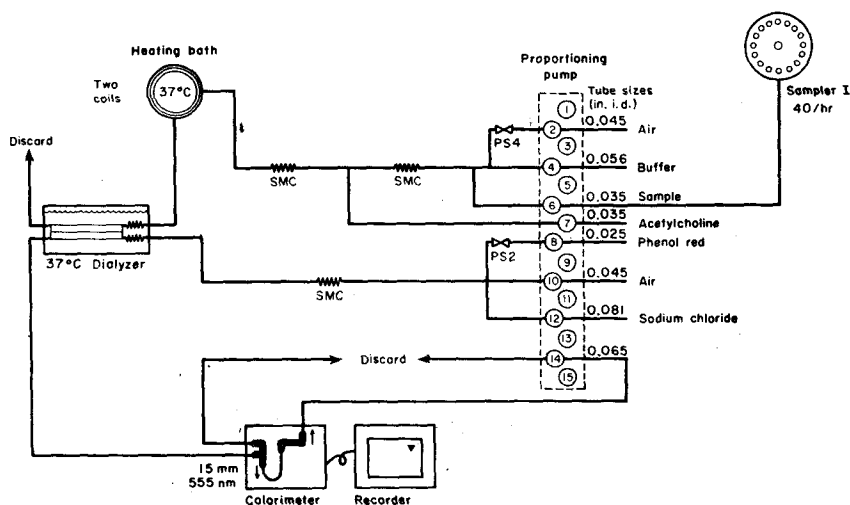


Fig. 5. Automated system for determination of ChE activity in microsamples and low activity media; PS = pulse suppressor and SMC = single mixing coil (redrawn from GAGE and LITCHFIELD 1967).

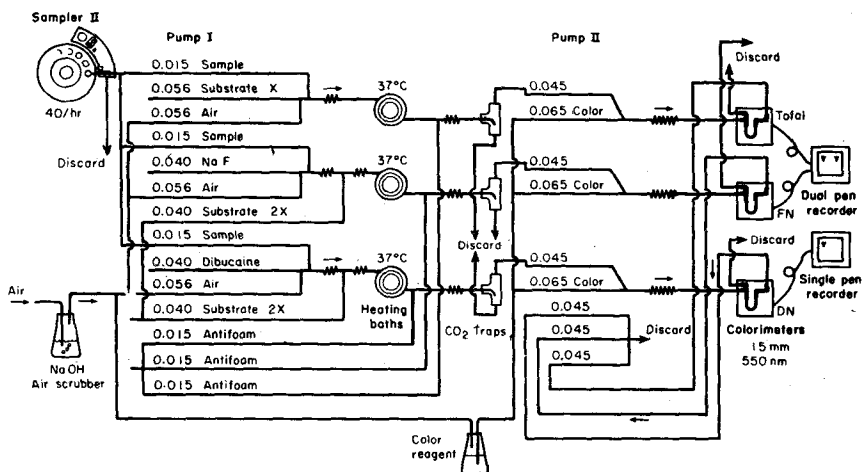


Fig. 6. Automated system for determination of three variants of human serum cholinesterases; pump tube sizes are expressed in in. id, Pumps I and II refer to pump number 1 and 2 rather than to pump types; substrate X = $2.5 \times 10^{-2}M$ acetylcholine bromide in buffer, substrate 2X = the same but at double concentration; provision must be made for filling the sampler wash chamber (redrawn from BOUTIN and BRODEUR 1970).

cide residue determinations. His review included most of the references cited above.

b) Diazotization and coupling analyzers

FRIESTAD (1967) developed a semiautomated method for diazotizable moieties (e.g., anilines and aromatic amines) from certain pesticides and with it described a method for the reproducible determination of linuron residues in soils as low as 0.1 ppm; 3,4-dichloro aniline was the analyte, produced by preliminary manual acid hydrolysis of Soxhlet extractives. The analyzer was shown also to determine azinphosmethyl, chlorpropham, methyl parathion, paraoxon, parathion, and propham. Some manual pretreatment was necessary in each case and varied depending upon whether the analyte was a nitro, carbamate, urea, or exceptional compound such as azinphosmethyl. The pretreatment variations were not discussed.

FRIESTAD (1974) slightly modified this AutoAnalyzer system for simplicity and used it in a rapid screening method for the detection of low residue levels (> 0.01 ppm) of linuron or of chlorpropham in carrots, potatoes, peas, and Swedish turnips. The method did not distinguish linuron from chlorpropham. Some interference at higher residue levels of monolinuron, propanil, and propham was predicted on the basis of recovery experiments with standard solutions of these compounds. Diuron, fenuron, and monuron were similarly evaluated; recoveries were so low as to indicate that these would contribute no significant interference surviving through the entire method. Preliminary sample manual operations in the method consisted of extraction of crop sample in acetonitrile and cleanup, following removal of most of the acetonitrile, by means of a slightly modified MILLS *et al.* (1963) procedure. A simple acid hydrolysis procedure, performed in oven-heated screw-cap sealed tubes, to convert parent compounds to their corresponding aniline moieties prior to presentation of sample solutions to the analyzer was also required. Evaluation of the entire method at a residue level of 0.07 ppm of linuron in field-grown, field-treated (pre-emergence) carrots resulted in a relative standard deviation of 10.8% calculated on the basis of six individual subsamples (50 g) from one bulk sample of homogenized carrots. Minimum detectability at 95% confidence limits for linuron in carrots, potatoes, peas, and Swedish turnips was about 0.01 ppm; that for chlorpropham was presumed to be at least as low, since the end-determinative system detected smaller amounts of 3-chloroaniline than of 3,4-dichloroaniline.

This basic residue method of FRIESTAD (1967) was modified and used for the determination of chlortoluron (a urea herbicide) residues in soils by GUTH *et al.* (1970) (Fig. 7). The entire residue method incorporated a manually-operated Bleidner apparatus (BLEIDNER *et al.* 1954, as modified by BAUNOK and GEISSBÜHLER 1968) for alkaline hydrolysis-distillation-extraction prior to presentation of samples to the AutoAnalyzer. The alkaline hydrolysis product of chlortoluron, 3-chloro-*p*-toluidine, was the