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Problems and Progress in Analytical Methods*

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Of all clean birds ye shall eat. But these . . . ye shall not eat: the eagle, and the ossifage, and the ospray, . . .

(Deuteronomy 14: 11–12)

In considering the general analytical background to trace contaminants in foods I propose first to review the analytical principles concerned and then briefly to outline some of the particular areas of interest in this field and the progress being made in solving them. In the context of the present meeting, contaminants are trace components. All trace analyses are characterized by the parameters of sensitivity and specificity, both of which broadly follow the indications and requirements of the toxicologist, though exceptions can be cited for each. Thus in DDT residue analysis, for example, it is now conventional to report separately *p,p'*-DDT, *p,p'*-DDE and (if present) *p,p'*-TDE and often to sum these residues as 'total equivalent DDT', even though the main toxicological consideration, for *Homo sapiens* if not for *Haliaeetus leucocephalus*, relates to *p,p'*-DDT or to technical DDT containing little or no DDE. This has been discussed elsewhere by Egan (1970) in relation to pesticide-residue levels in the total diet. In looking at the problems and progress I shall consider particularly selected areas of current interest, namely nitrates, nitrites and nitrosamines, polychlorobiphenyls and trace metals. In dealing with the general principles I shall consider in particular pesticide-residue analysis, although virtually every consideration in this field applies equally to other fields of trace analysis. Other aspects of nitrosamines, nitrites and nitrates, lead, mercury and other metals and pesticides will be dealt with by later contributors. I shall not consider polynuclear aromatic hydrocarbons, mycotoxins or technological contaminants arising incidentally from the treatment of food during processing and distribution, such as solvent or fumigant residues, or traces of surfactants, sterilants or disinfectants.

General principles

Problems and advances in pesticide-residue methodology have been reviewed recently by Gunther (1969). Looking, to begin with, at the general principles, we can accept for the moment that the first of these is that the sensitivity of the method used should match

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the requirements of the toxicological considerations. The general pattern in fact has been for the development of methods sensitive either to about 0·1 ppm or, in more recent years and where the circumstance called for greater sensitivity, to about 0·1 ppb*, give or take a power of ten either way in each case. The basic operations, illustrated here by pesticide residue analysis, are common to virtually all methods of trace analysis, although some elements of the sequence may be varied. These operations are sampling, laboratory subsampling, extraction of the residue, clean-up of the extract from co-extracted interfering substances, and detection, preliminary identification and estimation of the residue in the cleaned-up extract. Finally, where the identity of the residue is not known in advance of the analysis, the preliminary identification is confirmed using one or more independent methods of analytical approach. The latter is often a distinct operation which may be difficult for residues present in foods at levels of 1 ppm and is frequently exceedingly difficult at a level of 1 ppb. Apart from not always being easy, it is seldom cheap, in terms either of manpower or of equipment, to obtain an unambiguous positive identification at a level of 1 ppm. It is also necessary to have a clear understanding of the recovery factor, which sometimes assumes major importance when a residue method has to be used near its limit of detection. The exact application of general principles of residue analysis will vary according to individual circumstances; on whether, for example, the analysis relates to the evaluation of field research, to routine regulatory screening or to the enforcement of legal requirements.

With the development of the so-called 'multi-detection' or 'multi-residue' techniques based on chromatographic systems for pesticide-residue control, a new difficulty of collaborative study has been recognized in an area in which it becomes necessary to define an unusually large amount of subjective experimental detail. Collaborative study of such methods has proved to be possible in limited areas. However, a new feature, which in part has replaced the collaborative study, is the development of practical guidance manuals, and it has been pleasing to see a number of these developed for pesticide-residue analysis in recent years. Those produced in the USA by the Food and Drug Administration (1967) and the Department of Health, Education, and Welfare (Burchfield & Johnson, 1965) have now been followed in Canada by the Food and Drug Directorate's manual, edited by McLeod, Wales, Graham, Osadchuk & Bluman (1969). While these compendia do not necessarily set out to provide full information on all pesticides, most of them give comprehensive analytical guidance on a systematic basis. This is amply illustrated by the Canadian manual, which is designed to meet not only the strictly legal position in relation to established tolerances but also to cover residues arising from any established pesticide usage in Canada. This is done by flow diagrams illustrating the sequence of screening and determination procedures and supplementing a fully descriptive experimental text. The emphasis is practical throughout and bears particularly on broad multi-residue techniques for detection and estimation. Such manuals represent a substantial contribution to the advance of residue methodology and are not inappropriate to the position in Britain, where enforcement is basically at local government level and where central government provides a Pesticide Residue Analysis Information Service.

Chromatographic separation systems are frequently used not only for clean-up and estimation but also for preliminary identification of trace constituents. This is usually acceptable where the nature of the residue is known in advance, but there are distinct limitations in the extent to which different chromatographic methods should be regarded as giving

*b = 10⁹ throughout this paper.

independent support one to another. Elgar (1967) has given particular consideration to this aspect and has suggested four different parameters—gas-chromatographic retention volume, thin-layer chromatographic R_F value (or solvent partition p-value), gas-chromatographic retention time of a derivative formed by chemical reaction, and pesticidal activity against a susceptible organism—as alternatives for dealing with pesticide residues. Similar considerations apply to other types of unknown residues, although there is an obvious limitation in biological response where carcinogens are concerned. Not all methods are of equal value in the confirmation of identity, however. Completely unequivocal confirmation of the identity of unknown residues is possible by high resolution mass spectroscopy. This is a very sensitive as well as a very specific method of examination, but some purely practical difficulties may be encountered when this technique is applied to microgram (or sub-microgram) amounts, for example in conjunction with gas chromatography. It is also necessary to consider the way in which the data should be handled. Widmark (1969), for example, has suggested focusing the spectrometer at certain mass numbers and using it in this way as a general gas-chromatographic detector, if possible with alternation between two or more mass numbers to pin-point specificity. Ten selected mass numbers can be scanned at a rate of up to 10 sweeps/sec. Alternatively the whole mass spectrum can be scanned, using a mass marker, and recorded repetitively. Lovins (1969) has described the application of high-resolution mass spectrometry to the identification of individual organophosphorus and organochlorine compounds in mixtures. This method cannot at present distinguish structural isomers, such as dieldrin and endrin or p,p'-DDT and o,p'-DDT, but even this may prove possible if in addition an accurate measure of the relative intensities of the various ion fragments is possible. Biros (1970) has improved the sensitivity available from a mass spectrometric detector by making it possible to scan the column effluents rapidly without the loss of accuracy and reproducibility normally associated with the rapid recording of small ion currents; this is done by using a small laboratory time-averaging computer. He has applied this system to DDE- and dieldrin-residue analysis for quantities down to 1 μg.

Unequivocal knowledge of the identity of an 'unknown' residue is necessary for a full understanding of its significance before a principle of legal or health importance can be enunciated or a decision relating to an established principle made. The need for this is all the more apparent in the light of possible alternative (and misleading) constructions which could be put on the results of the simpler residue-analysis techniques. The limitations of the original pesticide-residue methods some 20 years ago, based for example on total organically-bound chlorine, were well recognized, although it is still necessary today to issue reminders from time to time that non-specific procedures should be used with caution (Egan, 1970). At the same time, general methods continue to have some use. Organophosphorus-pesticide residues are in general much less stable than those of the persistent organochlorine compounds and their detection, together with the detection of their breakdown products, presents a different and in some ways more difficult problem. There are a number of successful chromatographic approaches to this, but it is clearly unnecessary to use any of these if the substrate of interest can readily be shown to contain little or no organically bound (or total) phosphorus. This approach was used by Abbott, Crisp, Tarrant & Tatton (1970) in total-diet studies in Britain. It is also of course applicable to mercury.

Polychlorobiphenyls

As recognized by McCully & McKinley (1964), some of the early chromatographic analytical systems failed to distinguish adequately between dieldrin and p,p'-DDE. Inter-

ference in organochlorine-residue analysis by compounds of the polychlorobiphenyl (PCB) type was recognized by Roburn in 1965. Later Jensen (1966) found interference in pike to be due to these materials, and similar findings were reported by Holmes, Simmons & Tatton (1967) in predatory terrestrial birds and by Holden & Marsden (1967) in seals and porpoises. The PCB compounds have been widely used in industry, for example as transformer oils and as plasticizers for paints, lacquers and resins. For this reason they may present a special problem to the residue analyst; traces can derive even from simple packaging materials such as cardboard, as was recently pointed out by Bailey, Bunyan & Fishwick (1970). These authors were examining samples of ground cashew nuts, one of which appeared to contain about 10 ppm PCB; the same sample was found on closer examination to be the only one packed in a lacquered cardboard box.

PCB compounds are technical mixtures which contain many similar polychlorinated compounds. The chromatograms show a pattern of multiple peaks, a number of which may also correspond to those given by some of the commonly occurring organochlorine-pesticide residues, as was shown by Reynolds (1969). Such considerations led Risebrough, Reiche & Olcott (1969), for example, to conclude that some measurements of DDT residues reported earlier were too high. For a given PCB composition, the relative intensities of the peaks in the pattern may be substantially different. This problem can be tackled by separating PCBs (along with *p,p'*-DDE) from pesticide residues using a silica-gel column. To a first approximation the total PCB detector response as measured by the area under the chart peaks can be taken as the same as that for a similar amount of *p,p'*-DDE, and results can be expressed in this way. Koeman, Ten Noever de Brauw & de Vos (1969) based semi-quantitative PCB measurements on the height comparison with the peak $r_x = 1{\cdot}45$ using a particular commercial compound as the standard. Clearly it is possible only to estimate the order of the PCB residue, or of that PCB mixture which, after weathering or other manner of degradation, is present. It is nevertheless desirable to consider uniformity in the reporting procedure for PCB residues and this in fact has been the subject of recent proposals by the Organization for Economic Co-operation and Development.

Trace metals

Arsenic and lead have long been the subject of concern in relation to food, in which residues may arise both from natural and other sources. Both elements have been used in crop protection for over 100 years and the need to limit trace levels in materials used in the food industry was recognized more than 50 years ago. The general residue position has improved considerably in recent decades but a fuller understanding of the significance of the persistence of residues of some of the synthetic insecticides has stimulated a need to be aware of the possible build-up of inorganic residues where these materials are in regular use for pesticide, herbicide or defoliant purposes. The interest has extended to some other elements such as copper and mercury; and the fact that some of these now feature in organometallic combination has also meant that part of the interest may relate to the form in which the residue is present. Analytical chemistry has advanced considerably since the turn of the century, and while it would be wrong to dismiss lightly the ability of analysts in the nineteenth century, the practical application of trace analysis to every day need has improved enormously. It is perhaps worth remembering that, writing in 1819, Accum gave simple directions for the detection of 1 ppm lead in water. Today the method of choice for arsenic is based on the spectrophotometric procedure of Winkler (1962) which uses the reaction

between arsine and the silver salt of diethyl dithiocarbamate. As shown more recently by Bode & Hachmann (1968), a silver salt concentration of at least 20 μg/10 ml pyridine is necessary, the red complex formed being arsenic tri(diethyldithiocarbamate). The method is suitable for total arsenic estimation and has been used for the measurement of residues by Morrison (1969), who concluded that the levels in poultry tissues, soils and crops grown on litter-treated soils were unaffected by the use of litter from poultry houses where arsenical feeds had been used. Peden (1970), in a direct survey in Britain of 120 pig and other livers, found less than 0·1 ppm arsenic in all of the lamb, ox and calf livers and some 85% of the pig livers examined, with up to 1·0 ppm arsenic in about 10% and over 1·0 ppm in the remaining 5% of the pig livers. Some work has been done on chromatographic methods for separating organically-bound from inorganic arsenic but such methods have not been widely employed. Unlike the position with mercury, the general indication seems to be that organically-bound arsenic is the less toxic, at least to avian and mammalian species.

Trace mercury analysis has also long been a subject of interest in view of the toxic nature of this metal, although, somewhat surprisingly, it has in former times featured in pharmacopoeia preparations. The interest in mercury has increased sharply in recent years, initially as a result of industrial use of organomercurial compounds as fungicides in agriculture and the timber industry, and more recently by the recognition of its long-established use in the chlor-alkali industry (Somers & Smith, 1971). Serious local problems have arisen from the use of organomercurials for wood-pulp manufacture in Sweden and from their presence in industrial-manufacturing effluents in Japan. The high toxicity of methylmercury compounds, in particular, has encouraged the development of analytical methods based on the chromatographic separation and identification of individual organomercurials (or groups of organomercurials), and both thin-layer and gas-liquid chromatographic systems have been described. Atomic absorption spectroscopy can also be used, with a sensitivity of the order of 10 μg/ml or better. Cross checks by neutron activation analysis, a useful non-destructive method available for a number of additional trace elements, are also possible. Widmark (1968) has investigated the use of mass spectroscopy. A chromatographic approach less sensitive than mass spectrometry but nevertheless of considerable value because of its ability to distinguish the various forms of organically-bound mercury one from another and from inorganic mercury has been developed by Tatton & Wagstaffe (1969). This is based on the separation of organomercurial dithizonates and is sensitive to 2 μg. The dithizonates, which are self-indicating on thin-layer chromatoplates, are formed simply by shaking the extracted organomercurials in chloroform solution with dithizone. An even more sensitive procedure, down to 1 μg or less of mercury, is based on gas-chromatographic separation of the organomercurial dithizonates. Recent total diet studies by Abbott & Tatton (1970) in Britain show mercury levels of less than 0·02 ppm, as in Canada.

Provided the interest relates to the total residue, X-ray spectrometry, ultraviolet emission spectrography and atomic absorption spectrometry are all available for lead, copper and a number of other metals, the method of choice depending mainly on the sensitivity required. X-ray spectrometry is the least sensitive of the three methods but covers a wide range of elements, from sodium to uranium; the greatest sensitivity is for lead and the medium-heavy metals such as chromium, copper, iron, manganese and zinc. It can be applied directly to foods, for example to orange-juice concentrate for trace tin estimation; here the lower limit of detection is about 10 mg/kg, providing a method suitable for screening purposes. It can also be applied to the ash, either directly or in solution impregnated on to a paper disc. Surface-layer examination sensitivities are of the order of a few micrograms

for copper, iron and zinc. Ultraviolet emission spectrography, in which the sample material is subjected to an electric arc discharge and the emitted ultraviolet radiation is detected as a series of spectral lines on a photographic plate, can be applied to the estimation in food of all heavy metal residues with a limit of sensitivity of about 1 μg. Much of this work is now done by atomic absorption spectrometry, although the technique is still useful when several metals are simultaneously of interest. Atomic absorption spectrometry is very sensitive and is particularly suited to trace metal determinations in food. The sample is first ashed in order to prepare the necessary solution. Representative limits of detection are about 0·01 μg/ml for manganese, 0·03 μg/ml for beryllium, cadmium and zinc, 0·2 μg/ml for copper, chromium and lead and 1–2 μg/ml for aluminium, molybdenum and vanadium, the limitation usually being the amount of other salts present in the spray solution. Even greater sensitivities can be achieved if the element of interest is first selectively extracted from the ash solution, for example by chelation. Under these conditions concentration limits of 0·25 μg/ml for tin, about 0·004 μg/ml for chromium, nickel and lead and about 0·0005 μg/ml for cadmium and copper are possible.

Incidentally, Gorsuch (1970) has recently produced an excellent book on the destruction of organic matter, in which he deals individually with both wet oxidation and the ashing process for a wide range of metals and other elements.

Gas–liquid chromatography also offers useful possibilities if suitable volatile organometallic derivatives can be prepared. Foreman, Gough & Walker (1970) for example, have used beryllium β-diketones such as beryllium 1,1,1-trifluoroacetylacetone to determine this metal at levels down to 1 ng/ml in urine. The complex, which is thermally stable, is estimated using an electron capture detector. The possibility of using dicyclopentadienyltitanium chloride in a similar way has also been investigated and it should be possible to extend the technique to other metals of interest such as chromium.

Nitrates, nitrites and nitrosamines

Several different procedures are available for the estimation of traces of nitrite. The Griess-Ilosvay method for nitrite, based on diazotization of sulphanilic acid and coupling of the product with 1-naphthylamine, has been modified by Kamm, McKeown & Smith (1965) and subjected to close study by Kamm, Bray and Coffin (1968), who found it to give results which were statistically consistent and precise for various food substrates. A similar modification has been extended to nitrate in feeds by Schall & Hatcher (1969) using *N*-(1-naphthylethylene diamine) after reduction to nitrite, and an automated version of this technique for water analysis has been described by Henriksen (1965). Since 1-naphthylamine presents a carcinogenic hazard, the basic method has been further modified by Crosby (1967), who used the non-carcinogenic 1-naphthylamine-7-sulphonic acid (Cleve's acid) instead. Waters (1964), in a critical review of the direct methods available for the determination of nitrate in water, considered that no one method stood out as pre-eminent, a view also reached by Bunton & Crosby (1969), who extended the study to include ion-specific electrode methods. The latter authors concluded that the ion-specific electrode method gives more consistently satisfactory recoveries than the other methods. The diversity of procedures for nitrate is also reflected by the variety of official methods. Those in Britain include reduction to ammonia (titration) and nitration of xylenol (colorimetric). The American method, which depends on the formation of brucine nitrate (colorimetric), is identical with that recommended by the World Health Organization, but is subject to some interference by chloride; a second tentative method is based on ultraviolet spectrophotometry. In com-

paring the various methods, Bunton & Crosby (1969) concluded that the ion-specific electrode method is rapid and relatively inexpensive and can be used with confidence for the determination of nitrate in both natural and polluted waters, particularly in routine control examination for which the highest degree of accuracy may not be required.

Nitrate is an example of a pollutant which is partly of natural origin and partly otherwise; and as far as run-off nitrate is concerned, as much may be of natural origin as is derived from the use of nitrate fertilizer, even in arable farmland areas. It is less easy to state the position regarding the *N*-nitrosamines, although it is clear that where they occur this is almost certainly as the result of interaction between free secondary amine and nitrite. The analytical approach to traces of nitrosamines is basically classical and starts with extraction, clean-up of the extract by steam distillation, ion-exchange chromatography and solvent partition, followed by separation, detection, estimation and provisional identification by gas–liquid chromatography or polarography. This is a difficult area of trace analysis: it is one in which from 1 to 10 ppb of specific but not easily identifiable substances are of interest, when present in a very large excess of complex organic substrate which itself may include very many other largely unrelated trace as well as principal constituents. Extraction and clean-up processes in general call for individual consideration, according to the substrate of interest. Dichloromethane, and to a lesser extent acetone and acetonitrile are used for the extraction of volatile nitrosamines, but may give some difficulty with plant tissue; extracts must be carefully dried before bulk is reduced by evaporation. Steam distillation is a satisfactory clean-up technique but will obviously not apply to non-volatile nitrosamine. This also raises the question as to which individual compounds are of interest and how far the interest extends to non-volatile nitrosamines.

The unequivocal confirmation of the identity of the material estimated is particularly difficult. Polarography lacks specificity, although, like thin-layer chromatography, it can be particularly useful in a negative way. The use of two different gas–liquid chromatographic columns giving concordant results should be required; it might then be possible further to identify the peaks by an independent technique, such as the use of two different detectors. For unequivocal identification, however, detection by mass spectrometry is necessary. Several of the earlier reports of the detection of nitrosamine in biological substrates were based on the evidence of thin-layer chromatographic methods in which the separated chromatographic spots were rendered visible by a spray reagent. The methods described by Preussmann (1964) and by Preussmann, Neurath, Wulf-Lorentzen, Daiber & Hengy (1964) have been widely used. In the first of these the compounds are decomposed by ultraviolet irradiation and sprayed with sulphanilic acid/1-naphthylamine solution; in the second the spots are sprayed with aqueous ethanolic diphenylamine and palladium chloride and then irradiated with ultraviolet light. Neither reagent is entirely specific for nitrosamines; both however are very useful in the negative sense that the absence of a coloured spot is a good indication of the absence of nitrosamine. Spectrophotometric methods are normally limited to pure solutions and give a measure of the *N*-nitroso compounds which may be present. Polarography, used by Heath & Jarvis (1955), also gives a measure of the total *N*-nitroso compounds that may be present and is non-specific, although the reduction wave at about −0·9 v is given by all nitrosamines tested. It is useful as a rapid screening method and can be made somewhat more specific if, as shown by Walters, Johnson & Ray (1970), it is applied before and after ultraviolet photolysis, which decomposes the nitrosamine with the elimination of the polarographic wave. Photolysis rates differ for various nitrosamines, however. Daiber & Preussmann (1964) used this reaction as the basis for

nitrosamine estimation, measuring spectrophotometrically the increase in extinction of Griess-Ilosvay reagent. Gas-liquid chromatography is at present sensitive to about 1 ppm nitrosamine but current work is designed to improve this, for example by using better clean-up procedures (or more concentrated sample extracts) or more selective detectors. Nitrogen-specific detectors are obviously of interest here. Sen (1970) has recently taken advantage of the great sensitivity of the electron-capture detector to dimethylnitramine, the oxidation product of dimethylnitrosamine.

Conclusion

In the opening paragraph of this paper, I referred to the fact that while both sensitivity and specificity in trace analysis broadly follow the indications of toxicologists, this is not invariably so, and I used DDT and DDE as an example of specificity. Whereas 15–20 years ago the need in pesticide residue analysis was for greater sensitivity, this has, broadly speaking, now been adequately achieved, the main example being the persistent organochlorine insecticides. Indeed, there has on occasion been criticism that some of the analytical methods now available are too sensitive, and it is quite true, for example, that with routine chromatographic systems there is virtually no substrate in which 10 ppb DDT, if not $10/10^{12}$, cannot be detected. But it is possible that such orders of sensitivity may be required, or indeed may be inadequate, if the final decision on the safety of any chemical to which man is exposed is to be based on direct observation in man. This clearly is a subject which raises serious technical and ethical problems, as Magee (1970) has indicated. At the same time the Subcommittee on Environmental Improvement, Committee on Chemistry and Public Affairs, of the American Chemical Society (1969) has indicated that the identification and measurement of limiting nutrients in water would be greatly eased by improved analytical methods for low levels of phosphorus and various forms of nitrogen compounds. For the detection of some compounds and their metabolites there may in fact be a call for the development of even more sensitive analytical methods than are currently available.

> "It wasn't the words which frightened the birds,
> But the horrible *double entendre*."
> (Longford Reed)

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