officials, the draft is further revised if necessary.

It has been the policy of the section to contact the petitioner at this point and acquaint him or his representative with USDA's opinion on residue and give him an opportunity to concur or disagree with our findings. If he is able to clarify the residue picture with respect to any inability to render a favorable opinion, the matter is then re-examined and the final draft prepared.

The law requires that the opinion on residue which must accompany the certification of usefulness be forwarded to the Department of Health, Education, and Welfare within 30 days of the date the petition is filed. However, provision is made in the law for an additional 30 days, if required, for processing petitions.

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Requirements of Analytical Data

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PUBLIC LAW 518 of the 83rd Congress, familiarly known as the Miller Amendment to the Federal Food, Drug, and Cosmetic Act, embodies no new basic requirement. Original terms of the law, enacted in 1938, have always provided for tolerances for food additives that are necessary and unavoidable. The Miller Amendment simply recognizes the necessity of useful pesticides as a class, and affords a more convenient procedure for establishing tolerances for their residues on raw agricultural commodities.

Tolerances are not intended to concede entry into our food supply of any more residue than is entirely safe, nor any more than is consequent to good practice in employment of pesticides required for practical food production.

Safety of a residue is largely a consideration for the pharmacologist. How much residue may be consequent to good agricultural practice is a question the chemist must resolve from analyses of samples reflecting pesticide usage under representative conditions. He commonly receives them from the entomologist and others who conduct field tests and participate in other phases of the over-all study of the pesticide. The chemist occupies a central position in this study team. It becomes especially his obligation not only to coordinate his own work with that of his teammates but also to assure that they appropriately reciprocate. A prime requirement of the analytical data is that they be properly related both to toxicity considerations and to practical use of the pesticide.

It may seem unduly obvious to mention that the identity of the pesticide is one of the first facts to be pinned down. Yet frequent uncertainties in this respect are well known. Pesticides are not usually pure chemical entities. The nature of even substantial impurities is often incompletely defined. Some pesticides consist of more than one principal component in not-too-certain ratio. There are even instances where none of the components have been chemically identified. Such uncertainties can pose difficulties which, even if eventually surmountable, impede intelligent and purposeful study of both toxicity and residue potentiality.

A second point to be settled, as nearly at the outset as feasible, is the identity of the residue. That it is not necessarily the same as the chemical applied to the crop has long been recognized. To know the identity of the residue can be more important than knowing what the pesticide is; for the tolerance applies to the pesticide residue, to its toxicity and its quantity. Molecular change in an organic substance can make a profound difference in its toxicity. And such change can make the difference between suitability and unsuitability of an analytical method employed for residue determination. Some pesticides, for example, tend to convert to equally toxic epoxides, particularly when the residue is absorbed in plant or animal tissue. Methods for the parent compound do not detect its epoxide. In another direction, some of the pesticides, determinable by their *in vitro* anticholinesterase activity, tend to produce molecularly altered residues tremendously more reactive to this test. In cases such as these the analytical chemist could be under severe handicap by not knowing for what he is undertaking to analyze.

A useful indication as to whether the residue is or is not the same as its parent pesticide may often be obtained by check analysis with basically different methods—for example, by chemical analysis and by bioassay.

The next main consideration is the method for residue determination. Delicacy required of it will depend heavily on toxicity of the residue. The chemist must accordingly have the pharmacologist's guidance, in order intelligently to select, adapt, or devise an analytical procedure of suitable delicacy. In its details he will usually face the need to compromise to some degree. A method to determine an organic substance can seldom be strictly specific; not often is it wholly free from a sample blank, and variation therein; its efficiency of "recovery" is commonly less than perfect and not altogether constant. The method's utility depends on how satisfactorily, for the purpose at hand, such factors can be interadjusted and their variability controlled. This, of course, is nothing new to the analytical chemist; a method must always fit its purpose. The facts needed to satisfy him on this score are exactly the facts required to validate a method employed in acquiring data to support a tolerance proposal. Since variability limits the applicability of the method, experiments validating it need be replicated sufficiently to delineate the range of effect of that variability.

Residue data are obtained essentially for the purpose of ascertaining the relationship between quantity of pesticide applied to a crop and the maximum quantity of residue that may persist thereon at harvest. This is doubtless subject to many interacting influences, of varying prominence, and of varying effect from occasion to occasion. Among the more apparent are those of: growth dilution; ratio of crop surface to its mass; solubility, stability, and volatility of the deposit; degree of adsorption of it into subsurface tissue, or into surface exudates; and relative adhesiveness of formulation and of crop surface. It is evident that residue resultant from a

given mode, timing, and dosage of pesticide application will vary. The limit of variability, on the side of maximum residue, is the aspect of the relationship that is important to tolerance consideration. Adequacy of the data accordingly depends largely on how sufficiently, for the purpose, it is replicated.

There is no scientific basis on which to decide, *a priori*, how much replication is enough. Were it otherwise, one could be well on the road to evaluating data before obtaining them. If there exists a definable pattern of the relationship sought, and of its variability, that pattern will become evident at some stage in replication of the data. Previous experience affords only a crude idea of what that stage may be. We have not ordinarily been able to perceive such a pattern from fewer than 10 results; on occasion we have had many times that number without a satisfactory answer.

The degree of assurance with which harvest residue expectancy needs to be gaged will depend on related circumstances. For example, if it is a close question whether the maximum residue would or would not exceed the safe limit, that maximum needs to be estimated with comparative assurance. Other circumstances of the occasion may realistically bear on the degree of assurance needed and, therefore, dictate the extent to which replication must be carried.

The quality of the data has its significance. A mere additional analysis does not necessarily constitute a valid replication. Some sets of findings submitted in support of tolerance proposals have included results on samples reflective only remotely, if at all, of circumstances pertinent to the gaging of maximum harvest residue. Advantage should, of course, be taken of suitable samples wherever available, whether or not produced from field tests designed primarily for residue study. But it is ordinarily purposeless to analyze a sample of uncertain pesticide treatment, or one of history that patently contributes nothing to the problem of residue evaluation. Some such samples are going to become available, say, from early field tests of pesticidal effectiveness, at which time it may be impossible to decide whether they would be significant to the residue phase of the study. They will often be analyzed, rather than risk missing an opportunity. But, if in the light of later knowledge, those analyses turn out to be wasted, that fact must be recognized.

A common type of pesticide residue is that deposited and remaining strictly on an above-ground crop surface. With this type, at least, sets of data have often suggested a certain relationship between maximum residue and time interval subsequent to pesticide treatment. It tends to plot linearly on a semilogarithmic scale, as though the residue were subject to a decay process having a constant half-life. One may speculate, often with satisfying logic, as to the reasons for this; but without attempting to explain why it happens, we think it probably useful to know that it does happen, often enough to be worth anticipating in planning test programs. When such programs are initiated, the timing and dosage for a given formulation, needed for pesticidal effectiveness, or dictated by residue considerations, are ordinarily unknown. It is the purpose of the study to ascertain those facts. If it be anticipated that the maximum residue could exhibit a constant disappearance rate, it would seem practicable, without sacrifice of other purposes, to interadjust the dosage and timing of experimental treatments with a view to obtaining harvest samples the analyses of which will define any residue disappearance rate that may exist. Forethought on this point could minimize the number of analyses.

Considering Absorption

There are important modes of pesticides usage, and circumstances of usage that cannot, for physical reasons, contribute any appreciable residue unless it be incurred by absorption into the subsurface tissue of the crop. Soil usage is a common example of this. Ordinarily the dosage, when admixed with even a relatively shallow top layer of soil, represents a concentration therein which is itself measured only in parts per million. The amount of such soil mixture that could adhere to a marketable crop would not ordinarily represent a pesticide residue of any significant magnitude. The critical point to determine, therefore, is whether or not the pesticide absorbs into the crop. One may never safely assume that it does not; seemingly improbable instances of residue absorption are well known. The facts may often be best established from analyses of samples grown in plots receiving graduated pesticide dosage, extending well into a highly exaggerated range. If there is no absorption, the latter samples will provide persuasive evidence of the fact; if there is, the relationship between dosage and residue may prove highly useful in gaging the needed tolerance. There may be disturbing influences on such a relationship, of course. It may differ with different soil types and in consequence of other variables. Replication to cover a range of representative conditions is always needed.

The needs of the occasion are sometimes to show the absence of a residue, rather than to gage a required finite level of tolerance. Analysis is a tool of science designed to demonstrate the presence of a substance. It cannot directly show the complete absence of a residue. One means of adapting analysis to that purpose, however, is to establish the relationship of residue to decreasing pesticide dosage. By extrapolation, the dosage which contributes no residue may be ascertained. This approach has limited utility for proving absence of a residue if the residue is directly proportional to dosage. Not infrequently, however, the phenomenon of a threshold dosage exists, below which residue is not contributed, and for that reason this device should be considered when need to prove residue absence occurs.

Residue study of truly systemic pesticides is likely to be comparatively complex and extended. The residue is often a metabolite of the pesticide. It does diminish with time and does relate to dosage applied. Variability in these relationships is often a good deal greater than with surface residues. The chances are that conclusions regarding a systemic residue will require comparatively more data.

That is not to say, however, that there is anything simple or routine about residue studies in general. The required approach to each of them is one tailored by due consideration of all aspects of its own set of circumstances. The approach is not dictated by any fixed procedure nor are the data subject to any arbitrary requirements; they do not exist.

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