same considerations apply. The rate of uptake, rate of translocation within the plant, and site of possible concentration, are all vital data if the chemical is to be understood and properly utilized. Metabolism must be studied and metabolites identified and evaluated. These also are the responsibility of the chemist.

Soil fumigant chemicals including nematocides, pre- and post-emergence herbicides, and soil fungicides, must be studied to prove conclusively the questions of translocation, biological concentration, metabolism, and residues in the soil, as well as in food.

To summarize briefly, in order to develop economically a new organic compound which will adequately meet the government demands for safety to the general public, the organic chemist and biochemist must work together on the residue problem early in the development program. This will not only ensure greater financial success to the industry but will promote a better, safer future.

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The Opinion on Residue

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PUBLIC LAW 518, popularly known as the Miller Bill, is an amendment to the Federal Food, Drug, and Cosmetic Act, which empowers the Department of Health, Education, and Welfare to establish tolerances or exemptions from the requirement of tolerances in or on raw agricultural commodities destined for shipment in interstate commerce. This law assigns to the U. S. Department of Agriculture two responsibilities. A certification of usefulness of each pesticide chemical for which a tolerance or exemption is sought and an opinion as to the amount of residue likely to result on specified commodities. These responsibilities have been delegated to the Pesticide Regulation Section, Plant Pest Control Branch, Agricultural Research Service.

In regard to the opinion on residue, Public Law 518 reads as follows: "The Secretary shall submit to the Secretary of Health, Education, and Welfare with any certification of usefulness under this subsection an opinion, based upon the data before him, whether the tolerance or exemption proposed by the petitioner reasonably reflects the amount of residue likely to result when the pesticide chemical is used in the manner proposed for the purpose for which certification is made."

The regulations of the Plant Pest Control Branch include the following statement: "If a tolerance proposed by the petitioner is reasonably to reflect the amount of residue likely to result when a pesticide chemical is used, it must be large enough to include all residue which is likely to result when the pesticide chemical is used in the manner proposed by the petitioner, but not larger than needed for this purpose."

The Food and Drug Administration's regulations for the enforcement of Public Law 518 makes the following reference to the opinion on residue: "The tolerance thereinafter established ordinarily will not exceed that figure which the Secretary of Agriculture states in his opinion reasonably reflects the amounts of residues likely to result."

Information and Data Required in Petitions

Certain information and data are required to be a part of petitions and are necessary before the development of an opinion can be undertaken. This information includes: (1) chemical identity of pesticide, (2) proposed tolerances or exemptions, (3) detailed directions for use of the pesticide, (4) adequate residue data, and (5) a complete description of the analytical method or methods which were employed in obtaining the data.

It should be emphasized at this point that USDA's evaluation of methods and residue data contained in the petition and data otherwise available is solely for the purpose of providing a sound basis for an opinion on residue. In the process of establishing safe tolerances the Food and Drug Administration must recognize factors in addition to those taken into account by USDA in fulfilling its responsibility under the law.

The various types of methods commonly employed in obtaining residue data include biological assay, radioisotope, enzymatic, and chemical methods. The nature of the problem is such that sometimes results by two independent methods may be required. The chief advantages of biological assay and radioisotope methods lie in their sensitivity and relative freedom from interferences. A criticism is their lack of specificity. A number of specific and sensitive colorimetric and spectrophotometric methods have been developed for various pesticides which include insecticides, fungicides, herbicides, and certain antibiotics. Enzymatic methods have been developed and used to determine residues of organic phosphate insecticides or their metabolites. Examples of this type are those based upon the inhibition of acetylcholinesterases by these insecticides.

For a proper evaluation of a residue method, it is necessary to examine data from experiments specifically designed to establish the sensitivity, precision, and accuracy in the application to a particular substrate.

A meaningful way in which the sensitivity may be expressed is in terms of parts per million of sample, units generally employed for stating tolerances. It has been suggested that the sensitivity be stated as the smallest quantity of material that will give a detectable reading for some property such as light absorbance or transmittance, pH, or volume of titrating solution over and above that noted in a control or blank experiment in a total of nine out of 10 experiments. This would appear to be a precise expression of sensitivity.

Precision, of course, refers to the reproducibility of a method or a determination. Poor reproducibility with a method may be due to inherent weaknesses in the method, unusual variation in the composition of control samples, or to losses of the material sought in various steps of the analytical procedure—to mention a few causes.

Accuracy means the extent to which a given quantity of material can be

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accounted for by analytical determination. Accuracy of methods is demonstrated with recovery data which should be available. Recovery data should correspond to quantities of material in the vicinity of the proposed tolerance and to the quantity of residue likely to result following the recommended use of the pesticide.

These are some of the factors taken into consideration in the evaluation of methods. An excellent discussion of the problems encountered in securing quantitative residue data and the interpretation of these data was recently published by Gunther and Blinn (*2*). Also included is a discussion of the work of Decker (*1*), which involved a fundamental investigation of the questions of persistence and dissipation of various pesticide residues. Reference to this work has been extremely useful in providing information on the evaluation of methods and data. After examination of the data offered in support of the method to establish its validity for the purpose intended, we then proceed to an evaluation of the residue data.

Evaluation of Residue Data

It is of prime importance that residue data offered in support of proposed tolerances correspond as closely as possible to the dosage and application schedule that will appear on the labeling under directions for use. The directions for use should specify: (1) The type of formulation—dust, wettable powder, emulsifiable concentrate, or oil spray; (2) the dosage; (3) the method and details of application; (4) the number and frequency of applications; (5) interval in days between the last application and harvest. The proposed tolerance may take into consideration the reduction of residue by washing, brushing, or other effective means and if such is the case the directions for use should include such a statement. In so far as the data fail to conform to this pattern the difficulty in reaching an opinion increases. It then becomes necessary to resort to such measures as extrapolation, interpolation, or translation of results obtained under certain use conditions to use conditions contemplated. Such measures as those just mentioned, however, are fraught with uncertainties but these uncertainties can be held to a minimum if the factors which have been shown to influence the amount, persistence, and disappearance of pesticide residues are kept in mind.

In general, the resulting residue increases in amount as we go from dusts, wettable powders, and emulsifiable concentrates to oil sprays. For a given pesticide, dosage, and formulation, it is usually the interval between the last application and harvest that has the greatest effect on the amount of residue remaining at harvest. The presence of stickers or spreaders exert a pronounced effect upon the retention of the initial residue deposit.

Fleck (*3*), in a study of the rate of evaporation of DDT, concluded that the residual action of an insecticide is determined by its vapor pressure, its sticking power, its volatility, its absorption into the surface on which it is applied, and its resistance to chemical change. Decker concluded that vapor pressure alone was not an accurate measure of the loss of a volatile insecticide but that evaporation was the "summary effect of various factors which influence residue loss through vaporization." Decker's work under laboratory and field conditions was found to support such a conclusion.

Another conclusion reached by Decker in his studies on the dissipation of residues was that "residues resulting from different rates of application of a given substance will, under the same conditions of exposure, reach the vanishing or zero point at exactly the same time regardless of the magnitude of the original deposit." This finding can have practical usefulness in estimating the amount of residue remaining at a given time from a knowledge of the amount at some earlier time.

Gunther and coworkers have shown that the disappearance of at least some pesticide residues can be represented as a logarithmic function of time yielding a straight line characteristic of first order reactions. In a first order reaction the period of half-life is independent of the initial concentration and these workers have developed and made practical application of the concept of half-life in residue investigations.

Mention has been made earlier of the use of such measures as extrapolation, interpolation, and translation of data from one dosage or interval to another. There is reason to believe that residue results on one crop can be useful in interpreting or estimating the residues on a second closely related crop with similar physical growth characteristics. Consideration has been given to a grouping of various crops so that, within a group, residue levels on one or more crops might be predicted from directions for use and data on other crops in the same group. Such a classification has been proposed after considerable deliberation by the food protection committee of the National Research Council. This grouping has been useful in examining data in some petitions.

Draft of Opinion on Residue

After completion of our examination of the analytical methods employed for obtaining residue data and a study of the residue data on each raw agricultural commodity, an opinion is drafted. This draft can take one of several forms. It can be stated that the proposed tolerance reasonably reflects the amount of residue likely to result when the pesticide chemical is used as proposed or it may be concluded after examination of all pertinent information in the petition or from knowledge gained from past experience and other available information, that USDA can find no sound basis for an opinion as to whether the proposed tolerance reflects the amount of residue likely to result. Occasionally it has been our opinion that the proposed tolerance was either larger or smaller, by a certain factor, than the amount of residue likely to result. In other instances, our opinion has been limited to certain type formulations or modes of application in the absence of adequate data justify a more general conclusion.

At times, an unfavorable opinion will be tempered by a qualification that with a reduction in dosage or number of applications or if the interval between the last application and harvest is lengthened the proposed tolerance would then reasonably reflect the amount of residue likely to result.

When the draft of the opinion on residue has been reviewed by the section and revised in accordance with suggestions of our various specialists it is then discussed with professional scientists within USDA. Residue data from sources other than the petition itself but which are available to USDA must be reconciled with the findings from the petition at this time. These people, because of their knowledge of and their practical field experience with the pesticide and raw agricultural commodities in question, can frequently offer suggestions as to the amount of residue likely to result. After such conferences with USDA

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