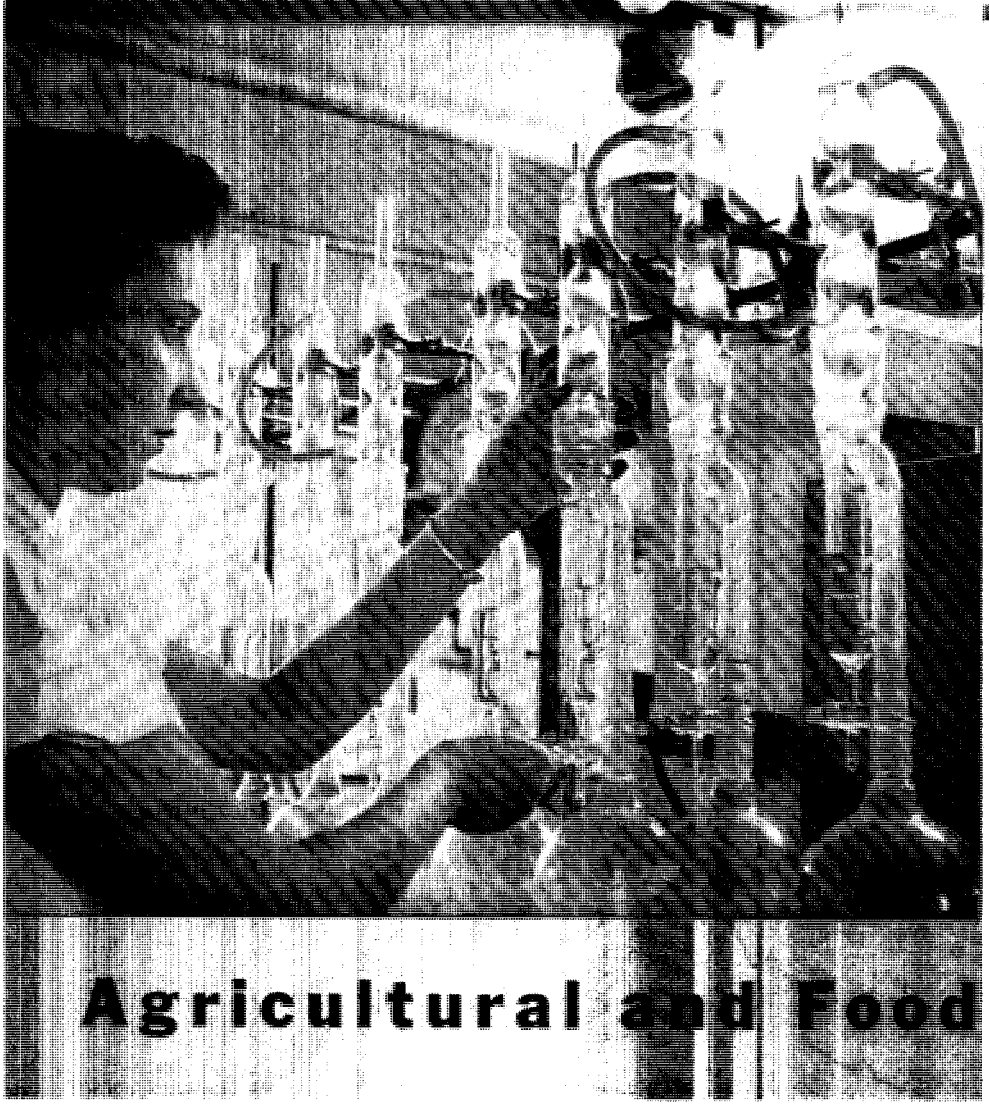

Agricultural and Food Chemicals

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discusses the procedures and economics involved in the biological evaluation of

THE TERM "FOOD CHEMICAL" is one of broad scope, ultimately including the basic concept that all foods are chemical. Not all chemicals are suitable for food, however, and this distinction has no relationship to their origin—i.e., natural or synthetic.

In the course of its evolution the animal kingdom has learned to be selective in its choice of foodstuffs, avoiding those which are not suitable regardless of their origin. Historically the human race, by trial and error, has learned to add chemicals to food to achieve preservation, or to enhance color, odor, or taste. Thus wines and vinegars, salt brines, wood smokes, certain coloring materials, and spices are almost universally accepted as suitable for addition to foods. This acceptance was based on necessity and experience, and was gained through direct experimentation on humans. So far as is known, the economic cost for biological evaluation was negligible but the returns were obviously great in terms of food supply. There is nothing new in foods' being chemicals nor in the concept of adding chemicals to food. What is radically different is the method of biological evaluation of the suitability of a specific chemical added to food and the economics involved.

It is not the objective of this discussion to establish the necessity or desirability of adding chemicals to foods, nor are we concerned with the various aspects of economic enhancement which this achieves. A recent compilation by the food protection committee of the National Research Council, however, lists some 550 different chemicals which may be deliberately added to food, including about 300 flavoring ingredients. In addition to these, there are numerous residues from pesticide chemicals, detergents, and other chemicals incidentally included during growing, storing, or processing. Such popularity must be deserved and it seems safe to assume that, in this country at least, the economics must be right. As used here the term "economics" is meant to include those of the chemical manufacturer, the farmer, the food processor and, above all, the public.

It should be completely obvious to those in the chemical industry that morally, legally, and economically there must be adequate control to enforce a standard of safety in the selection of suitable chemicals for addition to food. It is equally apparent that the original system of trial and error would be completely inadequate to meet any of these obligations. Federal food and drug laws are designed to provide the mechanism through which all interested parties may cooperate in research on, and the development, production, and use of food chemicals in an orderly, safe program.

From the standpoint of the biological scientist the fundamental concept in this law is that, while the human race cannot serve as its own test subject, accurate estimates can be achieved from studies on other members of the animal kingdom. The law places the responsibility for such estimates on experts qualified by training and experience to evaluate the safety of each candidate chemical. It is hoped that this discussion represents the concensus of all such experts in the field.

Additives to food arise from different sources, serve various purposes, and are accorded different status by the law. There are likewise some differences in the approach to their biological evaluation, depending on the inherent toxicity and the level

of exposure, but these are relatively minor in the total concept.

As might be anticipated, the discussion of the economic side of a biological evaluation program is much more difficult for a scientist than is the program itself. The question simply stated is this: how much will such a program cost. This is inevitably reminiscent of how deep is the ocean, how high is the sky, or how long is a string. Nevertheless, in the hope of getting some basis other than our own experience on which to supply an approximation, a very general questionnaire was sent to several representative laboratories experienced in this type of work and to some investigators who "farm out" such projects to independent laboratories, universities, and foundations. In essence the question was, how much did they feel must be allowed to cover the biological evaluation costs of a prospective food additive chemical. A sufficient number of replies was received to justify the broad generalities which will be quoted. Each chemical is an individual problem, however, and any cost estimate must be subject to revision at each stage of the investigation.

Analytical Method the First Problem

One of the first problems encountered in biological evaluation is an adequate analytical method for the candidate material, preferably a chemical method although a biological method may be satisfactory. A test tube method for the pure material is frequently not enough. The method must be capable of detecting the chemical in the presence of foodstuffs and often in biological materials such as blood, urine, and feces. Accuracy in the range of 1 p.p.m. is desirable and sometimes essential. The best talents of the chemist, biochemist, physiologist, and pharmacologist are sometimes taxed to find the original chemical or its derivatives, or to establish its complete degradation after exposure to that most amazing chemical factory, the animal body. Where legal tolerances apply, such a permissible quantity would be meaningless unless the amount actually present could be reliably determined. Hence the first problem involves the chemist, and the cost might well be estimated separately from the biological program.

Once in the biological science laboratory a chemical goes through certain preliminary programs directed at gaining an understanding of its fundamental properties. These usually include determination of its oral toxicity following single large doses. The results may be expressed as an LD_{50} (that amount which on a statistical basis might be expected to kill 50% of the animals exposed). The chemical may be added to the diet of rats at various levels for a period of 30 or more days in what may be called a subacute feeding test. Careful pharmacological observations during these preliminary tests may reveal characteristic responses suggesting specific types of action. If the results are encouraging, other species of animals may be employed, but such studies are rarely comprehensive in their design or execution. At the conclusion of such tests a new decision must be rendered before testing can be continued.

The law specifically prohibits the deliberate addition of a harmful or deleterious chemical to food. If preliminary evaluation indicates that the chemical has a rather high degree of toxicity, exerts a specific pharmacological effect, or causes alarming types of toxicity or pathology, its prompt abandonment as a deliberate additive is positively indicated. The cost may be only a few hundred dollars or, at most, a low four-figure sum.

If the preliminary results are not as clear-cut the problem facing research and management is much greater. It is the obligation of the biological team to outline carefully the various aspects involved in continuing the research. One of the first aspects to be reviewed is the purity of the chemical. As a general rule, further biological evaluation is not justified on a technical grade chemical, and every effort should be made to ensure that further studies employ only the purest available material and preferably the quality which will be proposed for marketing. Trace contaminants may materially alter the toxicity and pathology picture. Even entertaining the thought of marketing an impure chemical as a food additive is hazardous, particularly if the composition may vary in production. Assuming that the chemical identity, purity, and reproducibility are satisfactory, attention turns to a considered appraisal of the future prospects of the chemical for use in its projected field. While it is axiomatic that such properties as poisonous, toxic, harmful, or deleterious can only be evaluated in terms of use or exposure, it can also be stated dogmatically that at present there is no definition or guidepost, in either the law or its administration, upon which the pharmacologist can rely for advising management. This problem has been publicly discussed many times and recently reiterated by a committee of the National Research Council in its study of food colors. In the absence of such a reference point, the biological scientist relies on his knowledge and experience in appraising the future prospects of the new chemical.

After complete review of these preliminary data and all other aspects of the program, management must weigh the total picture and decide on one of two procedures. Either the program must be dropped or a commitment made to proceed with more detailed investigation. In the latter case the best analogy that comes to mind is a modern flight across the ocean. All known conditions have been evaluated and the flight is under way. As new and unexpected conditions arise it is possible, up to a point, to return to base. As the critical point of no return approaches, however, the final review of conditions then existent must determine the course to be followed.

Acute toxicity studies may give valuable information. Here rabbit is weighed before conducting study to determine dermal toxicity of experimental compound

In a properly designed biological evaluation program this course might well be described as a management financial commitment to follow a stepwise development program. With all the current information properly evaluated, the program director can make an estimate of the likely magnitude of this commitment at various key points along the way. The initial phase may be a short-term, intense study of the chemical—including dietary feeding, pathology, chemical studies on metabolism, and an estimate of the so-called "no effect" level under various conditions. This may cost as much as $10,000, a sum which certainly merits consideration of means to protect it against loss. One of the greatest protections against such loss is the saving of development time which can be built into the program but, like any protection against loss, there is an element of calculated risk or gamble. If the initial program is designed as an individual entity, it is destined to be an ultimate loss in both time and money for, even if favorable, the results will not be conclusive in themselves and the final, large-scale program must start at a later date. This has in the past been the most commonly used and recommended approach, briefly categorized as preliminary, subacute, and chronic.

More recently a redesigned program which gives proper perspective to the element of development time has found favor, particularly when the preliminary data made a reasonably favorable prognosis possible. In this design the short-term and long-term studies are initiated simultaneously, with sufficient animals to permit termination of groups at critical intervals. While starting costs are heavier the design is better, since both short-term and long-term data are analogous and there is more flexibility. More significant data are collected during the critical early period, and collateral studies such as hematology, urine analysis, organ function, and pathology are not duplicated. Since in either case the program can be terminated at any time, the net result is that by risking the heavier initial cost the experiment will be better, the cost will be no more, and the entire time of the short-term studies can be saved.

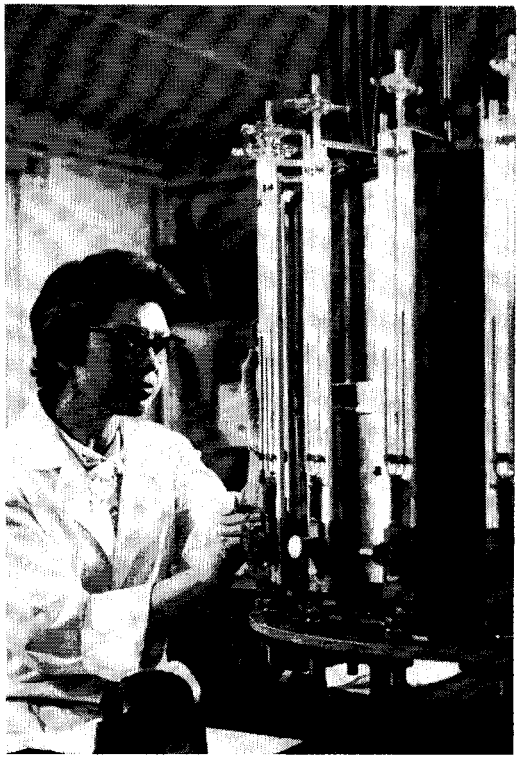
This applies to the basic chronic toxicity studies, but these are rarely, if ever, the only required evaluation. More and more the detailed study of the metabolism of the chemical in the body is paying off. Detailed discussion of this aspect is impossible within the scope of the present discussion, but inclusion of these studies, plus other modern tools such as radiotracers, tissue culture, pharmacological interaction, and reproduction, must all be carefully evaluated in the well-designed biological program. Including such of these collateral tools as may be useful, the final cost of biologically evaluating the suitability of a chemical for deliberate food use may well amount to a figure between $60,000 and $75,000. As indicated before, these are not fixed sums for "package deals." They are based on experience in various laboratories where, in some form or other, management has had to commit successive sums without assurance of the final outcome until the last item of data was in and evaluated. It is to be hoped, and reasonably anticipated, that as the knowledge of applied biological sciences expands, this design can be reduced in both time and money. In the meantime there is the obligation for both management and scientist to explore the newer approaches in detail so that the manifest benefits may be realized.

Food colors, for which there are separate regulations, are to be considered deliberate additives, to which the "toxic per se" doctrine is being applied. Recent regulatory activity in this field has centered attention on this concept, which is biologically untenable since it does not relate hazard or safety to use or exposure. The cost would be the same in either case so long as there is no improvement in methodology, but research and development is retarded because the biological scientist cannot evaluate such efforts with certainty under the present situation.

Thus far only deliberate food additive chemicals have been discussed. They serve as the most rigid prototype, and it is reasonable to expect that the economic considerations outlined would not be exceeded by other classes of additives. In contrast to the voluntary additives, those which occur unavoidably in industrial processing or as pesticide chemicals need not meet the vague criterion of not being poisonous or deleterious *per se*. Their safety

Tissue culture, long a scientific novelty, is proving a valuable tool in studying the effects of chemicals on human tissues

The Warburg respirometer is frequently used in enzyme studies such as in determinations of cholinesterase inhibitions by some of the newer organic pesticides



Small quantities of experimental compounds injected into chicken eggs may produce changes in embryos which help scientists understand the action of the compounds

or suitability for use is evaluated in terms of levels likely to be encountered under conditions of use, and provisions are made for setting tolerances. Each of these groups does, however, pose special problems, and individual consideration must be given to each candidate. In the case of pesticide chemicals the collection of the essential residue data may in itself represent an investment comparable in magnitude to the biological evaluation of safety.

Incidental additives which can be avoided, such as those used in packaging materials, are in general subject to the same routine of testing as deliberate additives but with the added problem of determining leaching characteristics. Positive proof of nonleaching properties would theoretically eliminate the necessity for biological evaluation, but it might be added that it takes real chemical ingenuity to prove a negative.

Around the world at the present moment interest in food additives centers primarily in food colors, pesticides, preservatives, antioxidants, and emulsifiers—in approximately that order. The stakes in progress, human well-being, nutrition, and market, are obviously great. The cost of progress is admittedly high in cash and, perhaps more importantly, in time. To those most experienced in the field the answer lies in research in methodology. Our basic knowledge is still running ahead of our applied experience, and this is as it should be. Nevertheless, a long-range view on the part of industry toward developing and validating new methods of safety evaluation will inevitably be a sound investment. The major problems can be delineated and the basic knowledge is available, but bringing the two together is a special research project for those who have the know-how on both sides. Until such research is given aggressive support the procedures and economics involved in biological evaluation of food chemicals will remain essentially static.

Potentiation

In November 1956 Food and Drug Administration personnel publicly revealed data which for some time had been discussed informally. These pertained to the "potentiation" of action when two organic phosphate insecticides were administered simultaneously to animals. The toxicity was greater than would be expected from the sum of the toxicity of each of the pair. In the meantime, in the *Federal Register* for Oct. 23, 1956, the official action of the Food and Drug Administration on this observation was published. In effect, the ruling was that no more tolerances would be granted for this class of pesticides under Section 408 of the law until evidence was provided that the newly proposed organic phosphate did not "potentiate" the action of any member of the class then having a permanent tolerance (five in all).

In spite of industry-wide and industry-government conferences, the evidence insisted upon by the regulatory officials requires pyramiding of experimental design, and hence cost, for each successive candidate. At least one petition for a tolerance on a new candidate has been officially filed and about four more are being evaluated for filing.

This obviously becomes an industry-wide problem since it involves the products of various companies and is common to all in the field. There is admittedly no evidence that the phenomenon of potentiation has any significance at the residue level or that all organic phosphate pesticides are involved. The gross approach to the problem now being employed does nothing to provide a workable understanding. Yet the cost of checking a new addition to the pyramid in the foreseeable future will far exceed the cost of the balance of the biological evaluation on the new chemical.

The phenomenon of potentiation is not new and there is no question but what an understanding of the mechanism involved in the current situation and its relation to pesticide residue safety could be achieved through a diversified basic research approach. Total cost would be less; the pyramiding would stop; all involved would profit. This is truly a wonderful opportunity for industry to take a new look at the way it is approaching the vital biological research and development aspect of its dollars-and-cents business.

I should like to change to the first person to summarize briefly, and to express a few personal convictions. There is no simple, stereotyped procedure to be followed in determining whether a particular chemical is safe and otherwise suitable for food use. Skill, ability, and a specialized viewpoint are the essence of success. There are many frustrating situations which constantly recur, and for which we all feel a satisfactory solution must be found. Nevertheless, after 16 years in this work and numerous visits to study the problem in other lands, I feel that we in this country are fortunate indeed. Our basic laws are sound and have proved workable. Where problems still exist progress is being made, and there is reason to assume that they will be solved. My personal view is that no necessary cost can be too high to achieve what we enjoy. Since biological evaluation is the ultimate determining factor, it is a fallacy to consider its costs as being something separate from other research and development costs. The total cost is the important item, and if this is too high after all permissible economies are achieved, then the food chemical must fail economically the same as any other venture in a competitive market. Only good management coupled with sound research and development can prevent this. I hope that the thoughts outlined here will be a contribution to such a team.

Based in part on a presentation before the Division of Chemical Marketing and Economics at the AMERICAN CHEMICAL SOCIETY'S *130th National Meeting in Atlantic City, September 1956.*