Table III. Residues (μg. per Gram) of Zoalene and ANOT after Withdrawal

Days after Withdrawal	Muscle		Liver	
	Zoal.	ANOT	Zoal.	ANOT
	PRETREATMENT: ZOALENE, 125 P.P.M. IN FEED FOR 8 WEEKS			
0	1.6	0.9	0.3	2.5
1	<0.1	0.2	<0.1	1.0
2	<0.1	<0.1	<0.1	<0.1
	PRETREATMENT: ZOALENE, 312 P.P.M. IN FEED FOR 8 WEEKS			
0	1.3	1.1	0.3	3.1
1	<0.1	0.2	<0.1	<0.1
2	<0.1	<0.1	<0.1	<0.1

Amprolium in liver tissue. How quickly the last trace of residue will disappear from the tissue after the removal of zoalene from the feed can be seen in Table III. Similar data are at hand for Amprolium.

Organic arsenicals showed identical behavior (Figure 4). The more toxic Arzene (arsenosobenzene) which contains trivalent As in an organic molecule killed 50% of the animals at 10 times the recommended level in 2 weeks. All growth was inhibited, but there was no marked accumulation of As in the tissue. The less toxic arsanilic acid (Progen) which contains pentavalent As was tolerated well even at the high level used in the feed. Although the total drug intake increased daily, the residue level in the tissue remained low. Once the compound was removed from the feed the tissue "dried off" quickly.

Figure 5 represents typical residue curves of feed additives in animal tissues. There is not a single feed additive known to the authors and used today in animal nutrition that would not follow this pattern. Experimental studies are at hand in the authors' laboratories for nitrofurazone, nitrophenid, and nicarbazin, as well as other coccidiostats. This is true also for antibiotics in feeds, as checked by the authors for aureomycin, terramycin, penicillin, and bacitracin, so long as the recommended and maximum level of 100 p.p.m. in the animal's tota ration is not exceeded. In higher concentrations, tetracyclines show a tendency for deposition in bone material but not in the soft tissue of the animal's carcass (*2, 3, 6*).

Figure 5 also demonstrates that tiny amounts of residues are unavoidable at the time of feeding as long as the feed additive will be absorbed from the intestine. The residue level will increase only slightly when the drug level in the feed is raised within certain limits. Contrary, however, to the steadily increasing total drug intake during longer feeding periods, residues in the tissues remain on a constant low level. Sometimes they even decrease, as in the case of Amprolium. Metabolites as degradation products of the drug should always be considered during analysis. Best information will often be obtained with labeled compounds.

Since livestock withstand several thousand times the drug level ever expected in human food derived from those animals, there is little or no chance for residue traces to jeopardize human health. There is no valid reason to assume that those traces will not be excreted by man as they are by millions of farm animals. This practical experiment, therefore, is of much greater significance in studying the safety of a feed additive than toxicity studies on rats, mice, cats, and dogs, performed only once or twice in a laboratory, could ever be.

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FEED ADDITIVES

The Additives Amendment in Practice

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THE FAMOUS "poison squad" experiments of the Wiley era in which young men served as test subjects created the misconception that all chemicals are harmful and the related idea that any amount of a chemical is poisonous (*6*). Thus, a struggle has been going on for over half a century between research and reason on one side and, on the other side, the emotional concept that all additives are harmful. The proponents of research and reason have included the land grant institutions, the U. S. Department of Agriculture, and the reputable food industry. It is comforting to realize that these proponents have generally prevailed over their adversaries who reiterated the misconceptions of the Wiley era. As a result, we are today enjoying a safe, wholesome food supply.

The 1938 revision of the original Pure Food Law probably constituted one of the finest pieces of legislation governing foods ever enacted into law anywhere in the world. The 1938 law gave broad authority to regulate the labeling of foods claiming special nutritive benefits.

In practice, the 1938 law had one flaw which Congress felt needed to be remedied—namely, it prohibited the addition in any quantity of any poisonous or deleterious substance to foods except where it was required or could not be avoided in food production. This particular flaw, it was widely felt, could not afford complete protection to the consumer, because prior establishment of the safety of an additive was not required. Furthermore, the flaw in the 1938 law also tended to retard technological advances in the food-processing field, since, any reputable manufacturer of chemicals, or any producer or processor of foods could not consider the use of a substance at any level if it was demonstrated to be poisonous at high levels, even though at low levels it might be safe and serve a useful purpose (*2*).

Prior to the enactment of the 1958 amendment to the Food, Drug, and

The major purpose of the Food Additives Amendment is to protect consumer health under the federal Food, Drug, and Cosmetic Act by prohibiting use of chemicals as intentional food additives unless such use is recognized by competent experts as safe, or unless adequate scientific test data (usually furnished by the sponsor of such a chemical) are available as a basis for establishing safety. An additional purpose of the amendment is to advance food technology by providing the mechanism for establishing safe tolerances for technically poisonous or deleterious substances which have functional value in processing or manufacturing practices. The Delaney clause in the amendment provides that no residue tolerance is allowable for any chemical used in or on a food or feed product if it is found to induce cancer when ingested by man or other animals. Technically, this provision is hindering food technological advancement, yet it contributes nothing to the safe use of food additives since hazardous use of any chemical is prohibited under the general provisions of the amendment.

Cosmetic Act, the only federal statute providing for the regulation of feed in interstate commerce was the original Food, Drug, and Cosmetic Act of 1906 which prohibited movement of adulterated or misbranded feeds. This paper gives a brief background of the Food Additives Amendment of 1958.

The wide use of new agricultural chemicals was stimulated during World War II largely by the control which these newer agents afforded over disease-borne pests in many parts of the world where our armed forces had to be protected.

The U. S. Department of Agriculture by law is charged with the responsibility of conducting research and collecting and disseminating information to serve as a guide to producers, processors, and distributors of food and feed. It was natural that the U. S. Department of Agriculture and our chemical industry should explore the use of these new chemical agents in food production. Indeed, there was an urgent need for vigorous effort to ensure an adequate food supply during and after World War II. Weeds, disease, parasites, insects, and other hazards along the food chain are estimated to limit our yields of crops and livestock by 120 million cropland acres—about one third of our 1959 harvest. In addition, demonstrated yield increases from the use of chemical fertilizers, and success in growth-promotion by the use of gibberellins, hormones, antibiotics, and arsenicals, suggest that vigorous exploration can further increase productive efficiency and possibly lower food costs for the consumer. The Federal Insecticide, Fungicide, and Rodenticide Act of 1947 defined the function of the U. S. Department of Agriculture in assuring a safe and wholesome food supply through the use of pesticides. Under Public Law 83–518, commonly referred to as the 1954 Miller Amendment to the Food, Drug, and Cosmetic Act, the Department of Agriculture was assigned the responsibility of developing recommendations for pesticide uses in agriculture which would be reliable, economical, and effective in food production. Under this same act, the Department of Health, Education, and Welfare was assigned the responsiblity of establishing safe tolerances for pesticides that might leave residues in or on raw agricultural commodities at the time of market. The U. S. Department of Agriculture's responsibility under the Miller Amendment was clearly defined, and the Department of Health, Education, and Welfare does not act upon a petition proposing a tolerance or exemption until the Secretary of Agriculture has issued a certificate of usefulness for the particular chemical in question. The author has dealt at some length with this background on federal laws regulating pesticides in a symposium concerned with feed additives because he feels strongly that if these respective responsibilities outlined above were defined in a similar way for chemicals used in manufactured feeds, which now come directly under the 1958 Food Additives Amendment of the Pure Food Law, some confusion might be avoided. Furthermore, it seems logical to assume that if the Department of Agriculture is knowledgeable regarding the usefulness of pesticides, it is equally knowledgeable regarding the use of chemicals in animal feeds.

The Food Additives Amendment to the Food, Drug, and Cosmetic Act, passed in 1958 after 6 years of intensive hearings, had a twofold purpose—to protect the health of consumers by requiring manufacturers of food additives, and also food processors, to pretest any potentially unsafe substances which are to be added to food and to advance food technology by permitting the use of food additives which are safe at levels of intended use. These purposes thus were intended to eliminate the flaw in the 1938 legislation which has already been referred to.

The concept of pretesting has received much attention. Safety requires proof of reasonable certainty that no harm will result to the health of man or animals from the proposed use of an additive. It was well recognized by Congress (*4*) that the test which should determine whether or not a particular additive could be used should be that of reasonable certainty in the minds of competent scientists that the additive would not be harmful to man or animals in its intended use. In this connection, the Congressional Record makes it clear that the Delaney clause, dealing with cancer-inducing substances, was inserted into the law to focus attention on the cancer-producing potentialities of many chemicals. However, such a focus was unnecessary since the Food Additives Amendment without this provision was aimed at preventing the addition to foods or feeds of any substance the ingestion of which would be expected to produce not only cancer but any disease of disability (*5*).

The specific provision in the law regarding cancer-inducing substances can conceivably prohibit the use of nutrients in foods or feeds. Biotin acts as a cocarcinogen in enhancing the liver cancer-inducing properties of azo dyes, so one could argue that its use as a vitamin supplement should be prohibited under the law. Likewise, selenium, as ammonium potassium selenide, produces liver cancer in experimental animals. There is evidence that this element may have a place in animal feeds in the control of white muscle disease in lambs. In this context, one can look upon the Delaney clause in the Food Additives Amendment as a measure which not only locks the door but throws away the key as well. In other words, under the Delaney clause if a given compound produces cancer at relatively high test-levels, one would not bother to investigate its possible significant biological effects at low levels. Thus, even under conditions in which no residues would remain, its use would be forbidden under the law.

It is not necessary to dwell further upon the Delaney clause of the Food

Additives Amendment in practice and the opinions of competent scientific bodies except to reaffirm that the Council on Foods and Nutrition of the American Medical Association (*3*) has pointed out that the Delaney clause, literally and broadly interpreted, does not make a demonstrable contribution to public safety.

In an appraisal of the Food Additives Amendment in practice, the magnitude of the problem created by the legislation should not be overlooked. During the 1958 Congressional hearings, it was estimated that 700 to 800 chemicals would fall into the classification of compounds which are generally regarded as safe based on experience of use prior to 1958. In the proposed and final listings of those substances generally recognized as safe, more than 700 had been identified as safe by the spring of 1961, but extensions were granted beyond March 6, 1960, for over 2000 compounds employed before 1958 in such a way as to bring them under the law (*1*). Thus, experience has indicated that the original estimates fell short of the actual numbers of compounds in use by a considerable amount. The corresponding legislation aimed at providing the regulatory agencies with additional scientific personnel was obviously geared to the estimate and, therefore, fell short of meeting the needs.

In an attempt to summarize what has been our experience with the Food Additives Amendment, the following aspects deserve specific mention: undue concern about carcinogens has forced testing and evaluation that might be directed more profitably elsewhere; excessive costs of pretesting may reduce the effort of industry to try new additives; and concern over contaminations of less than 0.1 p.p.m. of agricultural chemicals in certain foods, such as milk, is creating a real question as to whether or not these can actually be avoided under good production practices and whether or not strict enforcement may not adversely affect production.

Against these negative influences, one would list these positive aspects: there is increased emphasis on fundamental research, including a more thorough search for biologically-important compounds which occur naturally in foods and feeds; there is increased emphasis on chemical mechanisms in biological systems which can lead to biological control of pests of various kinds; there is increased emphasis on improvement of analytical techniques so that clearer understanding can be achieved as to degree of contamination of foodstuffs resulting from procedures of production and processing foods; and there is increased emphasis on research programs in educational institutions, government laboratories, and industry. Clearly, if the public, through its elected representatives, wishes effective legislation to ensure a safe food supply, it must also be willing to pay the costs of acquiring the necessary knowledge.

The negative aspects seem to emphasize human frailties or inadequacies, while the positive aspects point the way toward enlightenment or a pushing back of the frontiers of science. Although it may be costly in the long run, the positive should outweigh the negative aspects. We may find the way to reduce costs without sacrificing safety if the rule of reason can prevail.

We constitute the fortunate few in the world's population who have advanced beyond what is often referred to by certain extremists as natural farming, and we have, through science and technology, surrounded ourselves with an abundance and variety of foods. The extremists who would wish that we return to natural farming, that is, with no inorganic plant foods, pesticides, or chemical additives of any kind, are advocating for us regression toward the semistarvation situation prevalent among over half of the world's population which has not yet emerged beyond the natural farming stage.

If we can avoid harmful ways of using chemical additives, we need not concern ourselves unduly about the extremists. The record over the past few decades clearly indicates that it is when we disobey label warnings and use chemicals in harmful ways that we provide ammunition for the extremist. Wide public understanding of the facts about chemicals is essential if our farmers and the allied industries are to continue to supply us with an abundant and wholesome food supply. Every consumer should known that if we stopped using chemicals in the poultry industry, the price of eggs would rise 50 to 80%, and the supply would be greatly reduced. While most people are unanimous in the opinion that they want thorough pretesting to ensure against harmful use of chemicals in foods, we also want to be certain that the rule of reason prevails in deciding what is safe and what is not safe.

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