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REGISTRATION PATTERNS FOR AVICIDES

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Federal legislation relating to pesticide use in the United States dates back to 1910 with passage of the Federal Insecticide Act. This consumer protection from substandard or fraudulent products was considered sufficient for the next 37 years.

In 1947, Congress passed the Federal Insecticide, Fungicide, and Rodenticide Act. The FIFRA superseded the earlier legislation and was designed as a regulatory measure. Under the Act any product considered an "economic poison" must be registered with the U.S. Department of Agriculture before it may be marketed in interstate commerce.

The FIFRA defines an economic poison as any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any insects, rodents, nematodes, fungi, weeds, and other forms of plant or animal life or viruses, except viruses on or in living man or other animals, which the Secretary shall declare to be a pest, and any substance or mixture of substances intended for use as a plant regulator, defoliant or desiccant.

The Act brought rodenticides and rodent repellents under Federal law for the first time. The shortcomings of the Act, as related to the definition of "rodent," were soon obvious but it was not until 1961 that vertebrate animals other than rodents were included.

Pesticides registrations are handled by the Pesticides Regulation Division of USDA's Agricultural Research Service. The manufacturer is required to furnish statements of the composition of the product, the names of the crops on which it is to be used, the specific conditions under which it is to be applied as well as safety and efficacy data. Application for registration of economic poison under the Act may be made by a manufacturer, seller, shipper, or distributor.

Coverage of the 1947 Act was extended by the Nematocide, Plant Regulator, Defoliant, and Dessicant Amendment in 1959. Since 1960 these materials have been covered by the Amendment and registration requirements have been applied.

On December 20, 1961, a "Notice of Proposal to Declare certain Forms of Plant and Animal Life and Viruses to be Pests" was published in the Federal Register. This proposal was in accordance with authority granted to the Secretary of Agriculture under the basic law, wherein he is empowered to declare as pests forms of life not specifically named in the law.

This proposal was included in Regulations for the Enforcement of the FIFRA as amended August 29, 1964.

This declaration of pests includes:

Mammals - including but not limited to dogs, cats, moles, bats, wild carnivores, armadillos, and deer;
Birds - including but not limited to starlings, English sparrows, crows, and blackbirds;
Fishes - including but not limited to the jawless fishes such as the sea lamprey, the cartilaginous fishes such as the sharks, and the bony fishes such as the carp;
Amphibians and reptiles - including but not limited to poisonous snakes;
Aquatic and terrestrial invertebrates - including but not limited to slugs, snails, and crayfish;
Roots and other plant parts growing where not wanted; Viruses - other than those on or in living man or other animals.

Public Law 88-305, added in 1964, eliminated the "registration under protest" section which permitted the sale of an unregisterable product when a protest was filed. The amendment also specified that pesticide labels must bear a federal registration number. Other provisions related to conspicuous label precautions, and the removal of unwarranted safety claims from labels.

Supplementing the 1947 Act and its amendments and regulations is the Federal Food, Drug and Cosmetic Act of 1938.

This Act authorizes the Food and Drug Administration of the Department of Health, Education, and Welfare to set tolerances for residues of pesticides which may legally remain in or on food or feed. The following procedure is used for establishing tolerances.

1. When the manufacturer applies for registration of a product under the Federal Insecticide, Fungicide, and Rodenticide Act with directions for use on food or feed crops, or in a manner which is likely to result in residues on food or feed, he is informed that registration will not be issued until a finite tolerance or exemption is established.
2. The manufacturer must then assemble and submit to the Food and Drug Administration and to the Department of Agriculture; (a) Residue data conclusively showing the level of residues likely to result, and (b) toxicity data proving that such residues in or on food would be safe.
3. The Department of Agriculture evaluates the data and the proposed labeling and may certify to the Food and Drug Administration that the pesticide is useful for the proposed use and expresses an opinion on adequacy of the residue data. Specialists in the Food and Drug Administration then evaluate the toxicity data to determine if a tolerance is justified.
4. If residue and toxicity data are found to be adequate, the tolerance is established and the Department of Agriculture can issue registration. If the data are not determined to be adequate to justify the proposed tolerance, the Food and Drug Administration will refuse to establish the proposed tolerance and

may, should the data warrant such action, establish a tolerance at a lower level or a zero tolerance.

5. In the past, when a pesticide was registered for use on a food crop on the basis of a zero tolerance or on a no-residue basis, it meant that the directed use would not leave residues on the harvested food at levels which could be detected by chemical analysis. This has often meant that development of more sensitive test methods invalidated the zero tolerance or no-residue acceptance. This procedure has been abandoned in favor of registration on the basis of finite tolerances for all uses involving food or feed. Agricultural uses not involving food are considered nonfood uses and are registered in the absence of finite tolerances.

The review of petitions by the U.S. Department of Agriculture involves certification of usefulness and an opinion on the adequacy of residue data and proposed tolerance.

Data pertaining to efficacy are evaluated in relationship to proposed use of the pesticide formulation. Factors considered include effectiveness in controlling pests named in the labeling, and possible adverse side effects that directed use of the product might cause on the crop or animal to which it is to be applied. A thorough search and evaluation of data submitted, as well as other applicable data, is made. After such search, the specialist concerned with efficacy determines whether or not the proposed formulation would be useful for the intended use without causing significant adverse effects when applied according to the proposed labeling.

A memorandum to the Food and Drug Administration is prepared, either certifying that the proposed formulation would be useful or refusing to certify as warranted by the available data. Reviews of labeling and the application for registration are made at the same time and any required changes or comments relevant to the labeling are noted. In many cases, the Department will certify usefulness of the pesticide formulation for a proposed use, while requiring certain label changes or clarifying data to support registration of the product.

The petition proposes a finite tolerance level for residues of the pesticide chemical, including its metabolites and degradation products in the raw agricultural commodities involved. The chemist evaluates methods of analysis and residue data to determine the level of residue expected to result from the use proposed for each crop. If the data show that residue level is less than the proposed finite tolerance (but not unreasonably lower) a favorable opinion is given. Otherwise, an unfavorable opinion is given with an explanation as to how the data or a proposed tolerance are not adequate. A statement giving the required changes in directions for use or tolerance level that would be necessary is usually given. If the data show that no residue can be detected, a tolerance at "negligible" level is proposed, based upon sensitivity of the analytical method.

The review includes consideration of the residues of metabolites or degradation products, the mechanism by which the residues are dissipated, and their persistence on the crop or in the soil. Often residues resulting in plant parts other than the principal raw agricultural commodity must be considered. This is particularly important when such plant parts are likely to be used as forage for livestock.

ANALYTICAL RESIDUE METHODS

Each petition includes one or more analytical methods for determination of residues on the raw agricultural commodities involved. Recovery data must be submitted to establish validity of the method and to provide a means of estimating sensitivity. Ordinarily the sensitivity must be at least as low as 0.1 parts per million (ppm) and may be 0.01 ppm.

Gas chromatographic methods are most frequently used, although several colorimetric methods are published in the Official Methods of Analysis of the Association of Official Analytical Chemists 10th Ed. (1965). The Pesticide Analytical Manual, Volumes I and II, of the Food and Drug Administration lists other residue methods used for enforcement purposes. A summary, if not more detail, of the method is published when the tolerance is announced. Many methods, however, are developed for the specific purposes of developing data for the petition.

The Food and Drug Administration reviews methods to see whether the metabolites and degradation products are determined as well as the original pesticide. The specificity is particularly important in judging whether the method will be adequate for the enforcement program of the Food and Drug Administration. One requirement that may be difficult to judge is the completeness of extraction by a solvent. For the persistent chlorinated pesticides (aldrin, dieldrin, and endrin) gas chromatographic methods sensitive to about 0.01 ppm, are now used.

Once the necessary tolerance is established, the proposed product is acceptable for registration, if the specialists involved are convinced that the product can be used effectively and safely without leaving illegal residues on food or feed when all label warnings are followed. Registration by the U.S. Department of Agriculture is effective for a period of five years from date of registration, at which time, it is cancelled or extended for an additional five years.

The Miller Amendment to the Food, Drug, and Cosmetic Act, passed in 1954, provided that any raw agricultural commodity may be condemmed as adulterated if it contains a residue of any pesticide chemical, the safety of which has not been formally exempted, or which is present in excessive amounts. The Amendment gives the Secretary of Health, Education, and Welfare the power to establish residue tolerances.

The FIFRA and the Food, Drug, and Cosmetic Act, as amended, are interrelated by law and in practical operation. Most manufacturers file for registration and petition for a tolerance or an exemption from tolerance specification simultaneously.

The "Delaney Clause" of the FDCA, which stipulates that no material capable of causing cancer may under any condition be permitted in food, also affects pesticides registration.

Most states have pesticide registration laws specifying certain controls over distribution and sales of pesticides in intrastate commerce, as well as use and application laws governing the substances themselves. Modeled after the Federal Insecticide, Fungicide, and Rodenticide Act, the Uniform State Pesticide Act has been adopted in more or less similar form by 47 of the 50 states. State application and use laws differ greatly. Various states have regulations regarding licensing provisions, use of pesticides, and inspection of equipment.

It is obvious that current pesticide regulation legislation has cleared many hurdles. Paralleling this tortuous path has been the development of vertebrate animal

control chemicals. Avicides, while not demanding professional interest as early historically as rodenticides, have followed a similiar basic pattern of evolution. A good many of us are familiar with the initial mechnical methods of bird control as characterized by the scarecrow along with the use of firearms, firecrackers, carbide exploders, sticky bird repellents and dynamite in roosts. Earlier references indicate people being stationed in crop fields during critical periods and attempting to keep birds away by any method available.

As people and birds came into more open conflict, not only in agricultural but also in urban and suburban areas, it became obvious that more attention must be focused on the bird problem. Baiting techniques were developed and attempts were made to combine these techniques with bait materials specific for the pest bird. As with rodenticides highly toxic materials like thallium sulfate, 1080, and strychnine were used initially but the hazards associated with the use of these materials soon became obvious.

Label limitations like “For Professional Use Only" were instrumental in reducing some hazards. Of these more commonly recognized highly toxic chemicals only strychnine has been accepted for USDA registration. English sparrows and feral pigeons are the target animals for this registration pattern.

The professional bird control field has maintained a high interest level in highly toxic chemicals. Endrin and fenthion solutions for use in artificial perches were developed as one tool, while 4-amino pyridine (Avitrol) and 3-chloro-p-toluidine hydrochloride (Starlicide) maintained the interest in baiting techniques. The "Avitrol" and "Starlicide" approach indicated an interest in very specific bait materials while using the minimum level of active ingredient. Minimum levels can be accomplished by incorporating the active ingredient with each particle of bait or by blending a prepared concentrate with untreated grain.

The outlook for avicides seems to be radiating in three general directions. Some emphasis is being placed on the use of avicides in or on food or feed. The temporary permit for "Avitrol" use in field corn, supported by the necessary work in establishing a tolerance and acceptable chemical analytical method, is one example.

Basic concepts in bird control were modified and re-evaluated to formulate sodium fluoride for use in bird control. This re-evaluation produced increased interest in highly toxic compounds with emphasis placed on varied modes of action. Wetting agents and "Starlicide" are examples of bird control chemicals with varied actions.

Research in the area of bird chemosterilants has resulted in the registration of 20, 25-diazacholestenol dihydrochloride (Ornitrol) for use in suppressing feral pigeon populations. The type of research which produced "Ornitrol" is now being applied to other pest birds.

The outlook for avicides registration can be categorized by the mode of action of the avicide. This action in turn determines the minimum basic requirements for registering avicides.

Again, as with rodenticides, basic requirements for registering avicides are approached from the laboratory and field study viewpoint. The laboratory studies with dermal repellents must produce data which indicate physical-chemical properties of the candidate material as well as acute oral toxicities, subacute oral toxicities, acute dermal toxicities, and subacute dermal toxicities.

Field studies should be designed on the test-control area concept, pre- and post-treatment target population surveys, and show control success. If advanced field studies are in order, then these advanced studies should show the length of time treatment is effective and any variety in control success.

The following are some registration requirements for oral toxicants used in bird control.

A. Laboratory Studies
   1. Physical chemical properties.
   2. Acute oral toxicities.
   3. Sub-acute oral toxicities.
   4. Acute dermal toxicities.
   5. Sub-acute dermal toxicities.
   6. Cage tests.
      a. Single and multiple animal.
      b. Bait preference.
      c. Critical acceptance times.
      d. Bait stability.
   7. Secondary hazards.
   8. Hazards to non-target species.
   9. Specificity.
   10. Mode of action.

B. Field studies
   1. Preliminary
      a. Pre- and post-treatment population levels.
      b. Control success.
      c. Flock effect.
   2. Advanced
      a. Geographic areas on target species.
      b. Variety in control success.
      c. Significance in replications.

Most of the criteria listed above for dermal repellents and oral toxicants are also applicable as registration requirements for chemosterilants. However, data should also be submitted on specificity, reversibility, sex effected, and hazards to non-target species when dealing with chemosterilants.

DISCUSSION

J. KERLAN: In your opinion is dual testing of the toxicity of a product by USDA and FDA a duplication of research? You mentioned that in your talk. Secondly, in situations where there is disagreement between the two groups is the final decision delayed or can one department stop use?

J. LEE: Well, the basic toxicity data that is submitted with the application for registration of an economic poison and a petition for the establishment of tolerances

are the same data. The few oral toxicities for example which are arrived at in laboratory testing are submitted to both groups at the same time. They are sister petitions. The basic difference between the submission to FDA and to USDA is that FDA requires a three thousand dollar check to accompany their petition and we don't. The same data is used both places. In other words, if you establish acute oral toxicity, on albino rats for example, this data is acceptable to both agencies. You don't need to run two acute oral tests to satisfy the requirements.

G. GREENLEAF: I think this question really is, do the two branches then do tests that are duplicating?

J. LEE: No. We don't. We don't test any economic poison before the fact, before registration, and then mainly for efficacy and safety. In FDA the only duplication of testing that they do would be with the analytical methods that are submitted by the petitioner.

J. KERLAN: Would you answer my second question about a hypothetical case if there was disagreement between the two groups, could they stop use of that product?

J. LEE: Most areas are widely separated even though they are interrelated by law. The Food and Drug Administration is entirely responsible for establishing tolerance. The USDA is entirely responsible for registering the product. The way it goes, as I indicated in my talk, is that once the application for registration is submitted to us a petition is filed for the establishment of tolerance with FDA. These are two separate submissions; both containing similar data. We review the application for registration from a usefulness point of view and make comments to FDA on how acceptable the analytical methods are. FDA has the entire responsibility for establishing tolerance; we have nothing to do with that. There is not registration under FDA as such, merely the establishment of tolerance. There is no establishment of the tolerance under USDA as such, merely the registration of a product. While they work together, they are still separated.

J. STECKEL: If you approve one of these materials for the area in which you have responsibility, and FDA decides that they are not going to set a tolerance, then that is dead. There is nothing that is going to allow it to be re-evaluated without resubmission.

J. LEE: Well, the FDA can make suggestions back through us to the manufacturer that a slight change in the analytical method might result in more sensitivity which would permit support of the proposed tolerance. Avitrol is a good example. The efficacy data plus other requirements were submitted to us the same time the petition for proposed tolerance was submitted to FDA. The proposed tolerance is 0.1 parts per million of 4-amino-pyridine and its metabolites in commercially grown field corn. The sensitivity of the method is .04 parts per million, gas chromatographic analysis. If the tolerance is established at 0.1 ppm then that sensitivity of method will support it. If a tolerance is established at .01 the sensitivity of method will not support it, you see. Now the negligable residues of 4-amino-pyridine in meat, milk, or eggs is

not a consideration here. The proposal was to exempt these because 4-amino-pyridine could not be found in the corn prior to maturity.