VOL. 30, NO. 2 FEBRUARY 1975

Food Drug Cosmetic Law JOURNAL

Additional Papers Presented at the 18th Annual Educational Conference of the Food and Drug Law Institute, Inc. and the Food and Drug Administration

A COMMERCE CLEARING HOUSE PUBLICATION
PUBLISHED IN ASSOCIATION WITH THE FOOD AND DRUG LAW INSTITUTE, INC.

THE EDITORIAL POLICY of this JOURNAL is to record the progress of the law in the field of food, drugs and cosmetics, and to provide a constructive discussion of it, according to the highest professional standards. The FOOD DRUG COSMETIC LAW JOURNAL is the only forum for current discussion of such law and it renders an important public service, for it is an invaluable means (1) to create a better knowledge and understanding of food, drug and cosmetic law, (2) to promote its due operation and development and thus (3) to effectuate its great remedial purposes. In short: While this law receives normal legal, administrative and judicial consideration, there remains a basic need for its appropriate study as a fundamental law of the land; the JOURNAL is designed to satisfy that need. The editorial policy also is to allow frank discussion of food-drug-cosmetic issues. The views stated are those of the contributors and not necessarily those of the publishers. On this basis contributions and comments are invited.

The FOOD DRUG COSMETIC LAW JOURNAL is published monthly by Commerce Clearing House, Inc. Subscription price: 1 year, $25; single copies, $3. Editorial and business offices, 4025 W. Peterson Ave., Chicago, Ill. 60646. Printed in United States of America.

February, 1975

Volume 30 • Number 2

Second-class postage paid at Chicago, Illinois and at additional mailing offices.

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TO THE READER

Eighteenth Annual Educational Conference of the FDLI and FDA. The following papers were presented at the 18th Annual Educational Conference of the Food and Drug Law Institute, Inc., and the Food and Drug Administration, which was held in Washington, D. C. on December 3rd and 4th, 1974.

"Regulatory and Scientific Matters Currently Confronting the Animal Health and Nutrition Industry," beginning on page 85, discusses the challenges and problems faced by scientists in the industry and those in the regulatory agency. The article is written by *Dr. Raymond E. McKinley*, Assistant Director of the Department of Drug Regulatory Affairs in Hoffmann-LaRoche, Inc.

Dr. Howard R. Roberts, Acting Director for Management of the Bureau of Foods in the Food and Drug Administration, describes the progress that has been made toward both voluntary and mandatory nutrition labeling. His article, "Nutrition-Labeling Compliance," which begins on page 89, also explains the regulatory leeway permitted by the Agency because of the variability of different nutrients.

In his article, "USDA Plans, Priorities and Activities as They Affect the Food Industry and Consumers," *Dr. Harry C. Mussman* outlines the activities of the Department's Meat and Inspection Program in five areas—enhancement of the protein supply, chemical residues and additives, labeling and packaging, improvements in inspection methods, and microbiologic controls. Dr. Mussman, whose article begins on page 93, is Deputy Administrator in the Scientific and Technical Services of the Meat and Poultry Inspection Program in the Animal and Plant Health Inspection Service of the United States Department of Agriculture.

As Chairman of the Board of the National Association of Pharmaceutical Manufacturers, *Dr. Joseph Barrows* is in a position to know the complications that can arise when opposing medications are prescribed. His article, "Prescription Drug Labeling for Patients," beginning on page 98, gives examples of such complications while suggesting a compendium of drug reactions and interactions as one solution to this problem.

"What's New on the Horizon?" by *Dr. C. D. Van Houweling* cites the food shortage as an incentive to develop feed crisis substitutes. Weighing the risk of contamination against the benefit of increased food production, the Director of the Bureau of Veterinary Medicine in the Food and Drug Administration examines the ways to more efficiently convert plant protein to animal protein. The article begins on page 105.

Dr. George H. Gass in "A Discussion of Assay Sensitivity Methodology and Carcinogenic Potential" proposes that the Delaney Clause be reworded or reinterpreted to permit some residue—within a safety level—for each food additive. Dr. Gass is Director of the Endocrinologic Pharmacology Research Laboratory and a Professor in the Physiology Department and the School of Medicine at Southern Illinois University. His article begins on page 111.

Dr. David S. Salsburg, Senior Statistician in the Department of Clinical Research at Pfizer Central Research in Pfizer, Inc., reviews selected math-

ematical models and their use in determining safe levels of given chemicals. His article, entitled "Mantel-Bryan—Its Faults and Alternatives Available after Thirteen More Years of Experimentation," begins on page 116.

In his article, "Biological Perspectives on Approaches to Sensitivity of Analytical Methods for Tissue Residues," beginning on page 124, *Dr. Robert G. Zimbelman* discusses statistics and the reluctance of some scientists to use these research tools in conjunction with biological interpretations. Dr. Zimbelman is Research Manager of Reproduction and Physiology for the Agricultural Division of the Upjohn Company.

Heinz J. Eiermann is the author of the article, "Cosmetic Ingredient Labeling—A Status Report," which begins on page 129. In describing the rulemaking procedure for the Food and Drug Administration's order on cosmetic labeling, the Acting Director of the Division of Cosmetics Technology in the Office of Technology in the Bureau of Foods in the Food and Drug Administration gives examples of requirements for labels of various products.

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Food·Drug·Cosmetic Law
Journal

Regulatory and Scientific Matters Currently Confronting the Animal Health and Nutrition Industry

By RAYMOND E. McKINLEY

Dr. McKinley Is Assistant Director of the Department of Drug Regulatory Affairs in Hoffmann-La Roche, Inc.

IN THESE TIMES OF CRISES—such as the energy crises, the surge in rate of inflation, and now the worldwide food shortages—it should not be totally unexpected that there are currently several significant challenges that must be met by both the industry and the regulatory agency. As you will see, some of these are more regulatory than scientific in nature, but none may readily be separated from these major national and international problems.

Let me also emphasize that the list I am presenting is not intended as a total listing—rather I have tried to be selective in recognition of our time limitations for this program. Further, while I canvassed different acquaintances in industry for their suggestions, this listing represents my personal views and is not an attempt to present the views and policies of either the Animal Health Institute or Hoffmann-La Roche.

The following, then, is a list of regulatory and scientific matters that are, in my view, the most important.

(1) *Fully developed policies that provide reasonable and sound bases for benefit/risk decisions in the absence of total and complete scientific knowledge.*

The importance of this item is attested to by the latter half of today's program, which deals with one type of benefit/risk decision. I believe that ways must be found to permit judgmental decisions to be made in a timely fashion. In the face of the current national and international crises, we may not be able to continue to afford the luxury of years of investment of time and capital to enable significant animal drug developments to reach the marketplace. By the use of the term "judgmental" I in no way wish to imply that the approval of a new animal drug should not be based upon sound scientific data. I do believe, as do many of my colleagues in veterinary medicine and academia, that far too often today the final approvals get bogged down in bureaucratic red tape and scientific minutia when there is no fundamental scientific disagreement as to the safety and efficacy of the preparations. The tendency to substitute statistics for common sense or sound scientific judgment is just one example of this kind of problem.

(2) *Productivity increases.*

Despite the statutory requirements for regulatory agency action on New Animal Drug Applications (NADA's) within 180 days, it is a well-established fact that it is becoming rare to get an appropriate "incomplete" letter within that time frame, let alone receive an approval. It currently requires 8 weeks to process final printed labeling and publish the approving regulation, and it is not at all unusual to have this particular approving step take up to 6 months for completion. While I am confident that industry believes that the major corrective steps necessary to solve this problem must come from within the Agency, if there are ways that the industry can assist in providing solutions, it is a foregone conclusion that industry would be only too happy to consider and implement proper and appropriate actions. In any case, the present situation is contributing to the inflationary spiral, the energy crisis, and the food shortage.

(3) *Providing approved drugs for the so-called "minor" species.*

Prior to the passage of the 1962 amendments and the 1968 animal drug amendments, the requirements for approval were such that many drugs were made available for the treatment and prevention of disease for many species of animals, regardless of the size of the market.

Today the reverse situation exists. Approval of drugs for use in sheep, goats, ducks, fish, bees, etc., are conspicuously lacking. Several of these animal species make important contributions to our food supply and our agriculture industry, and collectively their importance is sizable. In my view, this is a regulatory and scientific problem that cannot be permitted to continue.

In the pesticide field the problem has been tackled through the IR_4 program, where the necessary efficacy and residue studies have been conducted under a grant system to various research institutions. It is the kind of problem that seems most amenable to solution through governmental coordination and leadership and will probably require action by both the United States Department of Agriculture (USDA) and the Food and Drug Administration (FDA). Since the solution to this problem will be in the best interests of the animal drug industry, the veterinary profession, the livestock industry, and the consumer, there is no doubt in my mind that these interested parties will willingly give their cooperation and support to any reasonable program.

(4) *Implementation of the Freedom of Information Act regulations and FDA's new policies which make public the agenda and other items discussed in conferences with FDA officials.*

The industry, in general, is very uncertain regarding these matters, since there seems to be, at the very least, an opportunity for premature release of confidential information. Several incidents have already occurred, illustrating how easily unintentional release of confidential information may occur. Furthermore, the new policies regarding conferences seem likely to severely restrict some important types of communications between industry and Agency officials. Such restrictions on the flow of information would not seem to be in the best interests of either consumers or industry. I regard this complex matter as a very important and difficult problem, and the complete solution is not yet in sight.

There is also another related matter associated with the implementation of new regulations and proposals. This is the concept that proposed regulations and policies may be implemented prior to their publication in final form or as final regulations. This practice seems to be contrary to the requirements of the Administrative Procedure Act and also would seem to have serious potential for creating inequality, confusion, and false starts. Since the Commissioner clearly has the authority to make major changes without consumer and in-

dustry input when emergencies or serious potential for harm to our human and animal population exist, it would seem that only in those circumstances should the Agency implement new rules without going through the usual proposal and comment periods of time It seems particularly appropriate to cite this issue in this forum provided by the Food and Drug Law Institute (FDLI).

While there may be other matters just as important which could be incorporated in this list, I have chosen as the final item:

(5) *Preparation of proposed regulations and policies.*

Far too often in recent times, proposals are pubished. albeit for comment, that appear not to have been well thought out and thoroughly evaluated with regard to their potential impact on either the Agency or the industry. I cite, as examples, the § 135.109 proposals, which, if enforced, require the submission of literally thousands of applications providing for the manufacture of the dilute or custom premix formulations. While this requirement has subsequently been changed via letters to individual companies, the incident demonstrates the problem. Similarly, there frequently seems to be a lack of appreciation by the Agency of the significant differences between human and animal drugs—thus some rules that may be totally defensible when applied to human drugs may cause undue burdens for animal drugs. All of this suggests that appropriate consultation with representatives of all affected parties prior to formal publication of proposals could very well be a constructive step and should be further considered by the Agency. **[The End]**

FDA PANEL FAVORS BAN ON ZIRCONIUM IN AEROSOL ANTIPERSPIRANTS

The Food and Drug Administration's Panel on Review of Antiperspirant Drug Products has declared that aerosol antiperspirants containing zirconium should not be sold until questions raised during research about the safety of zirconium-containing compounds have been adequately answered. The research has clearly shown, the Panel said, that zirconium chlorhydrate, the specific zirconium-containing moiety included in each of the antiperspirant complexes under review, will induce high-turnover skin granulomas (inflammatory reactions) in the epithelioid cell in man. The Panel noted that while it does not have undisputable evidence of granulomas induced by zirconium in the lung, it found the potential for such lung diseases to be an extremely serious one.

CCH Food Drug Cosmetic Law Reporter, ¶ 41,271

Nutrition-Labeling Compliance

By HOWARD R. ROBERTS

Dr. Roberts Is Acting Director for Management of the Bureau of Foods in the Food and Drug Administration.

ONE OF THE PRIMARY RECOMMENDATIONS resulting from the 1969 White House Conference on Food, Nutrition and Health was that nutrition information should be increased in food labeling. This recommendation was adopted as a major objective of the Food and Drug Administration (FDA). Five years, several ulcers and three *Federal Register* notices later, nutrition labeling is today essentially a reality.

For those cases in which nutrition labeling is mandatory, such as instances where nutrients have been added to products and/or where nutrition claims are made for the product, industry estimates indicate new labels are ready for about 95 percent of the products. Considerable progress has also been made with products for which nutrition labeling is voluntary; estimates range from 40 to 50 percent of affected food items.

Overall Progress

The overall progress in nutrition labeling is shown not only by the commitment of such major producers as Del Monte, Pillsbury, Libby, Kellogg, General Mills, General Foods, Campbell and Green Giant but also by the private label efforts of supermarket chains such as Safeway, Giant, Grand Union and First National. Nutrition information now appears on the labels of virtually every type of processed food, and at least one chain, Giant, has provided generalized nutrition information, on posters and handouts, for fresh produce.

An informal FDA survey in July of this year revealed nutrition labeling on 361 items, produced by 66 different companies, in Washington area supermarkets.

Although the nutrition-labeling regulations are not yet effective, the FDA conducted a limited survey in the first part of this year to assess the initial degree of compliance. Out of 150 samples collected, only ten had label format and/or nutrient content discrepancies, four of which were significant enough to formally alert the involved companies. This is a very gratifying degree of compliance —particularly at this stage of the game.

Rousing Success

The increasing frequency of nutrition labeling and the demonstrated success in complying with FDA regulations, together with pleasant surprises as to the costs involved, indicate a rousing success for nutrition labeling.

With such success, why did the FDA decide to postpone the effective date for nutrition labeling from December 31, 1974 to June 30, 1975? There are those who imply that this is just another case of the FDA bowing to industry demands. This charge is, of course, patently ridiculous. The fact of the matter is that genuine industry problems involving scarcity of ingredients, delays in obtaining equipment and decreased sales resulted in unused label inventories. In addition, the label changes required by the omnibus food-labeling regulations have somewhat overwhelmed label and package suppliers. Initially, we felt that we could deal with these problems on a case-by-case basis. However, it soon became apparent that problems were sufficiently widespread to warrant a blanket extension. If we had not provided this extension of the effective date, thousands of dollars would have been lost because of the need to replace deviating labels. In addition, thousands of dollars worth of foodstuffs would have had to be withheld from commerce for destruction or, at least, relabeling (costs which the consumer would ultimately have to bear). More importantly, the building momentum toward voluntary nutrition labeling would have been lost.

Pockets of Resistance

Despite the progress that has been made, there are still isolated pockets of resistance to nutrition labeling. This resistance is due, in large part, to a lack of understanding of the compliance requirements. It is said by some that nutrient levels are too variable to permit accurate labeling and that the acquisition of nutrient data is too expensive.

Actually, variability is specifically considered in the regulations for both added (Class I) and natural (Class II) nutrients. Several allowances are made for variability in natural nutrients. First, nutrition labeling in this case is voluntary, providing nutrition claims are not made. In addition, compliance is required only at a minimum of 80 percent of the label claim or, in the case of calories, carbohydrates and fat content, only at a maximum of 120 percent of the label claim.

Other allowances for variability applicable to either Class I or Class II nutrients include basing compliance checks on the average nutrient level in a sample, rather than on individual units, and the use of an incremental system for listing percentages of the U. S. recommended daily allowances (RDAs). Finally, allowance is also made for the variability inherent in the analytical methods for nutrient determination.

Indicated Nutrient Levels

The compliance rules, which are statistically based, are designed to allow flexibility to the producer within the confines of good manufacturing practice while at the same time assuring the consumer of receiving products with the indicated nutrient levels.

As a "rule of thumb," a producer has virtual assurance that a lot will be in compliance provided that the label value is no greater than about 95 percent of the lot average in the Class I (added nutrient) case. For example, if the lot average is 11 percent of the U. S. RDA, a label value of 10 percent assures consistent compliance. Note that since only 10 or 15 percent label values are permitted, the 10 percent level is the value of choice anyway. For the natural nutrients, the rule of thumb is to label at the average level for each nutrient, subject to the permitted labeling increments.

With these kinds of compliance provisions, nutrient testing need not be extensive. For example, running complete nutrient profiles for products that contain significant amounts of only a few nutrients is a waste of time and money. Further, testing to determine whether 16 percent or 17 percent of the U. S. RDA is more representative of the product is also a waste of time since the 15 percent U. S. RDA labeling increment would have to be used anyway.

Nationwide Field Program

In summary, nutrition labeling is now a fact of life with mandatory situations well in hand and voluntary labeling becoming commonplace. To borrow a phrase from the past, I want to make it perfectly clear that the FDA does not intend to back off from finalizing the nutrition-labeling regulations—they will become effective July 1, 1975. In addition, we will fulfill our obligation to enforce those regulations. We have already planned and will implement a nationwide field program to check compliance with these regulations starting on the effective date July 1, 1975. In addition, we have in draft form a proposal addressing nutrition labeling of fresh fruits and vegetables. This proposal, about which we will solicit public comment and data, will be completed in priority order after the Dietary Supplements (80.1) regulation and the "Low-Calorie" (125.6) regulation.

What then is the next step in the nutrition-labeling program? The best answer to that question is the one word, education. Almost everyone, I believe, would agree that nutrition labeling cannot completely succeed without substantial strides in nutrition education. That, however, is a subject in itself. I will therefore close with a quote from the Commissioner which summarizes our commitment:

"... we found that our current program for relabeling foods with nutritional information has necessarily meant a re-education of essentially everyone involved with food marketing, and must eventually involve education of the entire public. Otherwise the full potential of the program will not be realized. We are trying to take on this massive effort, step-by-step. We will be several years at the task."

[The End]

FDA PROPOSES TO DELETE LABELING EXEMPTIONS FOR TEN DRUGS

Full disclosure labeling exemptions for dispensing packages of ten prescription drugs for which directions, hazards, warnings, and use information are commonly known to practitioners should be revoked, the Food and Drug Administration (FDA) has decided. In a proposal to delete the exemptions, the agency said that labeling requirements included in Drug Efficacy Study Implementation (DESI) notices for the drugs have superseded the specific exemptions previously granted. Later monographs to be prepared according to procedures now being developed will set forth conditions under which drugs that are not "new drugs" will be deemed safe and effective and not misbranded. These "old drug monographs" will supersede exemptions for drugs not the subject of DESI notices. Comments on the proposal may be filed with the FDA until March 25, 1975.

CCH Food Drug Cosmetic Law Reporter, ¶ 45,246

USDA Plans, Priorities and Activities as They Affect the Food Industry and Consumers

By HARRY C. MUSSMAN

Dr. Mussman Is Deputy Administrator in the Scientific and Technical Services of the Meat and Poultry Inspection Program in the Animal and Plant Health Inspection Service of the USDA.

MANY IN THE AUDIENCE TODAY are not familiar with the extensive food inspection role played by the Meat and Poultry Inspection Program of the United States Department of Agriculture (USDA). In brief, the legislation which mandates the Program requires that all meat animals destined to move in commerce as food be examined both antemortem and postmortem. Further, all products prepared from these animals must be free from adulteration and labeled in such a way as not to be misleading.

With approximately 130 million red meat animals and 3 billion poultry being processed during a year's time, the job is a large one. Because of the rapidly changing technology in the industry, the job is constantly being evaluated and modified to reflect the Program's receptive attitude toward change—as long as consumer protection is not compromised.

Understandably, a full list of Meat and Poultry Inspection Program plans, priorities and activities for the next year would be rather lengthy. Therefore, I have selected only a few of those considered most important for purposes of discussion today. I'll be touching on five areas: enhancement of the protein supply, chemical residues and additives, labeling and packaging, improvements in inspection methods and microbiologic controls.

Enhancement of the Protein Supply

In this era of worldwide food shortages, we believe it is incumbent on us in the USDA to encourage the fullest possible utilization of protein from both animals and plants. Consequently, wherever possible, we will act favorably on proposals for the broader use of various protein sources on the condition that nutritional quality of the final product is maintained.

For example, this coming year we hope to publish rules covering the preparation, quality control, and composition requirements of mechanically deboned meat and poultry. We plan to include provisions covering the use and labeling of any product which fails to comply with minimum protein or maximum fat requirements.

Other areas of protein recovery and utilization we will be looking into this year are the use of the residue from low and high temperature rendering, recovery of protein fractions from broths and stocks, the use of animal blood protein, protein recovered from the cooking of bones, and lastly, the use of plant proteins. This latter area has already been given much attention in our program and will continue to be an important consideration.

Chemical Residues and Additives

As you may know, an expert panel of distinguished scientists has been working for a year on the nitrite-nitrosamine problem as it relates to cured meat products. The panel has made recommendations which the Department will receive and be acting upon in the near future. Very briefly, the recommendations were to: (1) eliminate nitrate in all products except dry-cured products and fermented sausage; (2) reduce to 156 parts per million (ppm) the nitrite used in various products except for the dry cure which will remain at 624 ppm pending additional research; and (3) reduce the allowable residual nitrite to 125 ppm for cured primal cuts and canned cured perishable or shelf-stable product, 100 ppm for cooked sausages, and 50 ppm for canned cured sterile product. No action was taken on bacon due to a planned joint industry/government study of high ascorbate-low nitrite levels. This study, and another covering fermented sausage, will be completed in the months ahead.

In order to more effectively determine the incidence of chemical and drug residues in animal tissues, we plan to broaden the scope of our monitoring program by including at least four more compounds among those for which we routinely check. We will be working closely with the Food and Drug Administration (FDA) in establishing priorities.

Labeling and Packaging

We view truthful, informative labeling as one of our primary responsibilities and as an area where many improvements are expected in the months ahead.

Nutrition Labeling: Approximately 65 companies are now actively engaged in nutrition labeling and over 150 kinds of product labels, including sausage, pizzas, luncheon meats, and many canned products, have been approved. Over a year ago, we published proposed regulations to which most consumers, consumer representatives, and industry representatives have responded favorably. Final regulations will be published shortly. They will include provisions for sampling based on volume produced so that the cost borne by large and small manufacturers for verifying the nutritional character of a product will not be disproportionate. They will also make available an alternate method for determining the protein contribution of a product, expressed as a percentage—the U. S. RDA (recommended daily allowance). This change was prompted by the concern expressed about the determination of the protein contribution using protein efficiency ratios.

One further item with respect to nutrition labeling: Through a joint industry, consumer, and government task force, we are actively considering the possibility of using standard nutrition values for a number of products. If we can do this, the cost for such labeling can be significantly reduced.

Percentage Labeling: We are considering proposing regulations for percentage labeling of characterizing ingredients in meat and poultry products. They would be similar to those adopted by the FDA for other food products. Labeling and standards of composition problems for such products as patties, poultry rolls, meat and gravy, and main dish foods might be resolved through the use of percentage labeling.

Net Weight: We are continuing to confer with the FDA, the National Bureau of Standards, and other agencies within the Department to formulate compatible net weight procedures and standards for all food products. In the meantime, the Department plans to issue a revision of its earlier proposal and take into account the divergent viewpoints expressed on this rather controversial matter. As before, the proposal will contain provisions for determining net weight compliance outside of the official plant—in the marketplace.

Flexible Retortable Pouches: We expect to move ahead this year on the packaging of retortable products in flexible plastic materials.

A Program bulletin has been issued and letters have been sent to persons and firms who expressed an interest in this type of packaging, inviting them to submit their applications for review. Based upon the acceptability of information received, we will grant approval for test runs. No final decision will be made, of course, until we know that the packaging material is chemically safe and that the packages will hold up during handling and/or abuse in the marketplace.

Improvements in Inspection Methods

It is imperative that we make the most efficient and effective use of our resources. Never has the determination to do so been as strong as it is now. Consequently, high among our priorities is the development of better ways of doing our job of inspection. These are some of the more important projects we will be working on during this year.

Trichina: Trichinosis cannot be detected with absolute certainty in swine using conventional inspection techniques. This means that all pork products which may be eaten in the home without thorough cooking must be specially treated in the processing plant to destroy any live trichina. We have entered into a contract with the Los Alamos Atomic Energy Commission Laboratory to develop a low-cost, rapid, sensitive, and specific test for detecting trichina-infected swine during postmortem inspection. The work done so far is extremely promising and we expect to complete much of the developmental work on a testing system this year.

Cysticercosis: For another parasitic disease, beef tapeworm, we have available a costly but imperfect means of detection during postmortem inspection. We have started work on a serological test for detection which is less costly than the present method and more effective.

Quality Control Approach: Our current method of surveillance of the processing of meat and poultry products after slaughter is effective, but it requires a heavy expenditure of manpower. We are encouraging processors to develop their own quality control programs which we will then monitor at a considerable savings in manpower. We expect to have the new monitoring system in operation in several plants before the year is out. Training of inspectors to staff these plants is now in progress.

New Procedures: The postmortem inspection of poultry is an extremely high-speed operation. Through time studies we have found that many inspectors are functioning at workloads which could, if carried out too long, impair their effectiveness. Consequently, we have started working to develop new, simplified inspection proce-

dures which represent a significant departure from current practices and which will permit lower inspection workloads without reducing inspection effectiveness. We have been conducting pilot studies in turkey plants this fall and will proceed with the tests in broiler plants over the next several months.

Microbiologic Controls

Many meat and poultry products are highly perishable and can be the source of food poisoning outbreaks as the result of mishandling, particularly the holding at temperatures which permit the growth of spoilage and disease-causing organisms. We do not believe it is possible to eliminate these organisms entirely. Therefore, we are directing our efforts toward education of the consumer and food handlers in how to prepare and store meat and poultry products properly. We are also taking a close look at how meat and poultry products are handled in the processing plants with a view to reducing the numbers and kinds of micro-organisms associated with good operating practices. Two major projects come to mind where we will be working this year:

Microbiologic Guidelines: We are developing microbiologic guidelines for various meat and poultry products and hope to publish those for frozen meat and poultry pies and beef with gravy in the near future. Other guidelines are being developed. Having available these guidelines will give us a benchmark against which we can review product operating and handling procedures.

Salmonella: Meat and poultry products are frequently implicated in a rather widespread form of food poisoning—salmonellosis. Salmonella are sometimes present in the intestinal tracts of animals slaughtered for food and become a contaminant of meat or poultry during slaughter. We have now organized two joint industry-government task forces—one covering meat and the other poultry—for the purpose of analyzing the problem, in all of its aspects, and making recommendations for corrective measures. These two task forces will be moving ahead during the year.

In conclusion, I should like to simply reiterate a point I made earlier. The large, dynamic industry we regulate requires that we have a program capable of adapting and changing quickly. In this way we can modify inspection procedures and practices that promote the dynamism of the industry and also introduce the many regulatory innovations which fulfill our mandate to do what is necessary to protect the consumer. **[The End]**

Prescription Drug Labeling for Patients

By JOSEPH BARROWS

Dr. Barrows Is Chairman of the Board of the National Association of Pharmaceutical Manufacturers.

DURING THE PAST DECADE, there has been an increasing awareness of the clinical problems that result because one drug alters the therapeutic response to another that is administered concurrently. Reports of such interactions now consistently appear in medical and pharmaceutical literature.

Drug Reactions

There are many reasons for this increased concern of drug interactions. The most obvious reason is that 18 to 30 percent of patients in hospitals have a drug reaction or interaction; that drug reactions account for 3 to 5 percent of all hospital admissions; and that 30 percent of patients admitted for a drug reaction have a reaction to the same or another drug during the same hospitalization. Patients with reactions have a considerably longer stay in the hospital (11.4 days without reaction and 28.7 days with reaction). The economic consequences of drug reactions in hospitals are staggering when the average patient stay of 12 days is increased to 14 days because of drug reactions occurring within the hospital. The estimated dollar cost of such hospitalization alone is approximately three billion dollars per year.

In approximately 29 percent of the patients, the reactions are severe. The most discouraging finding is that most of these reactions are avoidable especially in hospitalized patients where the patient's chart and work-up are available to the physicians in attendance.

Concurrent Prescriptions

Imagine the incidence of drug reactions and interactions outside of the hospital-physician controlled area. The poignant reason is the absence of a patient profile system established nationwide, coupled with the fact that many individuals are taking more than one potent drug concurrently prescribed to them, often by two practitioners. It is difficult for one physician to learn completely what medications have been prescribed for a patient by another physician, if indeed the patient has informed the practitioner that he is seeing another physician and/or that he is taking an analgesic or cold tablet which he purchased without a prescription, since he is likely to equate the terms "drug" or "medication" with prescribed medication.

Most data on drug reactions have become available only recently. Drug reactions have increased in number and severity because of the increased availability of potent prescription drugs. In addition, increased physician and patient awareness has assisted in compiling this data.

Equally important is the difficulty in relating cause and effect presented by drug reaction consisting of one agent diminishing the effect of a second agent. In fact, whenever a compound fails to produce expected results, alteration in its absorption, metabolism, or elimination should be considered.

Physician Awareness

Since drug interactions are the sequelae attending the simultaneous use of two or more drugs, educating the physician to routinely investigate the patient's present drug regimen is paramount to any system of safeguards against drug reactions or interactions. Sequential to alerting the physician to ascertain the drug regimen of his patients, the physician must have a ready reference under the heading of the drug he wishes to prescribe such as:

Drug to be prescribed "Chloramphenicol"
Incompatible with:

(1) Aminophylline
(2) Barbiturates
(3) Cephalothin
(4) Dimenhydrinate
(5) Diphenhydramine
(6) Diphenylhydantoin
(7) Erythromycin
(8) Hydrocortisone
(9) Hydroxyzine
(10) Polymixin-B
(11) Prochlorperazine
(12) Protein Hydrolysates
(13) Sulfadiazine
(14) Sulfisoxazole
(15) Tetracyclines
(16) Vancomycin
(17) B Complex Vitamins
(18) Tolbutamide

Certainly there are clinical instances where a patient needs therapy of two opposing drugs. The practitioner, however, must first be aware that the drugs can cause serious consequences if dosage adjustment is not prescribed to compensate for the altered response due to drug interaction ; and such therapy should be closely monitored.

Drug Reaction Compendium

A pincer approach is therefore necessary to educate the health professions by composing and disseminating a compendium of drug reactions and interactions; and secondly by implementing a patient package-insert system.

The criteria for selection of drugs must encompass:

(1) *Drugs Having Opposing Pharmacological Effects*

Example: Pilocarpine eye drops for a patient who is taking an anticholinergic preparation prescribed by another physician for a gastrointestinal condition.

(2) *Drugs Having Similar Pharmacological Effects*

Example: The increased central nervous system depressant effect that is experienced by individuals being treated with sedative-hypnotic drugs or tranquilizers when they consume alcoholic beverages.

(3) *Alteration of Gastrointestinal Absorption*

Example: A change in the pH of the gastrointestinal contents may also cause another type of problem. For example, oral dosage enteric-coated laxative tablets or other enteric-coated medicaments should not be given orally within an hour of antacid therapy because an increase in the pH of the gastrointestinal contents may effect the disintegration of the enteric-coated tablet in the stomach.

In addition, complexation may inhibit absorption of drugs.

Example: Tetracycline can combine with metal ions such as calcium, magnesium and aluminum in the gastrointestinal tract to form complexes that are poorly absorbed. Thus, the administration of certain dietary items (such as milk containing calcium or antacids containing aluminum salts) to patients on tetracycline therapy could cause a significant decrease in the amount of tetracycline absorbed.

(4) *Drugs Which Stimulate Metabolism*

There are many drugs, such as phenobarbital, that are known to increase the activity of liver microsomal enzymes (enzyme induction).

Example: It has been shown that the rate of metabolism of the coumarin anticoagulants is increased in patients also being treated with phenobarbital. The result of this interaction would be a decreased response to the anticoagulant since it is being more rapidly metabolized and excreted, possibly leading to an increased risk of thrombus formation if the interaction is not recognized.

Phenobarbital can also stimulate the metabolism of diphenylhydantoin.

Pyridoxine given concurrently with L-dopa lowers the blood levels of L-dopa by speeding up its peripheral decarboxylation.

(5) *Drugs Which Inhibit Metabolism*

There have been many reports of drug interactions involving the use of monoamine oxidase inhibitor with another drug or with certain dietary items.

Example: The Xanthine oxidase inhibitor, allopurinol, has been found useful in the treatment of gout. However, it is important to recognize that this enzyme is involved in the metabolism of such potentially toxic drugs as mercaptopurine and azathioprine and when it is inhibited the effect of the latter agents can be markedly increased.

(6) *Displacement of Drugs from Protein-Binding Sites*

An interaction of this type may occur when two drugs that are capable of binding to proteins are administered concurrently. Since there is only a limited number of protein-binding sites, a competition will exist and the drug that has greater affinity for the binding sites will displace the other from plasma or tissue proteins.

Example: Both phenylbutazone and warfarin are bound to plasma proteins. However, apparently phenylbutazone has a greater affinity for the binding sites, resulting in a displacement of the warfarin, making increased quantities of the free drug available. In this situation, hemorrhaging could result.

(7) *Alteration of Urinary Excretion*

The alteration of urinary pH, either done intentionally or unknowingly, can influence the activity of certain drugs. For example, acidifying agents are administered with methenamine to enhance its antibacterial activity.

The urinary pH will influence the ionization of weak acids and weak bases and thus affect the extent to which these agents are reabsorbed or excreted.

A recent report calls attention to the possible development of quinidine toxicity when the urine becomes alkaline in disease or during alkalinizing therapy. The excretion of quinidine was shown to decrease considerably as the urinary pH was raised.

It has been known for many years that probenecid can increase the serum levels and prolong the activity of penicillin derivatives by blocking their tubular excretion. Probenecid (Benemid) also inhibits the excretion of other drugs such as indomethacin (Indocin). Phenylbutazine interferes with the excretion of acetobexamide (Dymelor). Salicylates excretion is inhibited by furosemide (Lasix).

(8) *Interactions at the Adrenergic Neuron*

Monoamine oxidase (MAO) functions to break down catecholamines. When it is inhibited, increased levels of norepinephrine within the adrenergic neurons result.

If amphetamine is administered to a patient whose stores of norepinephrine have been increased by MAO inhibition, he may experience severe headache, hypertension (possibly a hypertensive crisis) and cardiac arrhythmias.

Interactions of this type have been well documented. One report has described the development of agitation, fever (temperature to 109.4°), coma and convulsions in a patient that occurred as a result of the ingestion of tranylcypromine plus a capsule containing dextroamphetamine sulfate and amobarbital.

Although most sympathomimetic amines, such as amphetamine, are available only by prescription, others such as ephedrine, phenylephrine and phenylpropanolamine are found in many popular over-the-counter (OTC) cold and allergy products. Certainly it would be wise for patients being treated with MAO inhibitors (Isocarboxazid (Marplan), Nialamide (Niamid), Phenelzine (Nardil), Tranylcypromine (Parnate), and Pargyline (Eutonyl)) to avoid using products containing these agents.

Hypertensive crisis has occurred in people being treated with MAO inhibitors following the ingestion of certain foods having a high tyramine content, such as pickled herring, certain cheeses and alcoholic beverages.

(9) *Alteration of Electrolyte Levels*

Excessive loss of potassium is one of the problems associated with the use of many of the newer diuretics (thiazides). This may

present a problem for patients being treated with digitalis derivatives, many of whom would be candidates for diuretic therapy (congestive heart failure). If a potassium loss remains uncorrected, the heart may become more sensitive to the cardiac glycoside and arrhythmia might result. Prolonged corticosteroid therapy and cathartics may also lead to hypokalemia and cause similar problems.

(10) *Antibiotic Antagonism*

If a bacteriostatic agent that will stop cell multiplication by a mechanism other than one which leads to cell death, is given concurrently, the penicillin derivative cannot exert a bactericidal effect because the cells are no longer mutiplying.

One study compared the use of penicillin with the use of penicillin and chlortetracycline in combination in the treatment of pneumococcal meningitis. The results disclosed a 79 percent mortality rate in patients treated with penicillin and chlortetracycline as compared to a 30 percent mortality rate in the patients treated with penicillin alone.

(11) *Alteration of the Gastrointestinal Flora*

A number of anti-infective agents have been reported to enhance the effect of simultaneously administered anticoagulants. It has been suggested that this effect probably develops as a result of interference by the anti-infective agent with the production of Vitamin K by micro-organisms in the gastrointestinal tract. Broad-spectrum antibiotics, such as the tetracyclines and chloramphenicol, and anti-infective agents that are used to reduce the intestinal bacterial flora (such as neomycin, succinylsulfathiazole) are most likely to cause problems of this type. Penicillin derivatives, sulfonamides and probably other antibiotics also may show similar effects.

These are only a few of the mechanisms by which drug interactions develop, but they may act as a starting point for the development and implementation of a meaningful approach to educating the health-care community and the public.

Pertinent to the success of diminishing drug interactions or drug reactions is an accurate compendium composed in a format which is conducive for quick reference both by generic and trademark name, which should be disseminated to all in the health-care profession.

Preliminary to discussing the types of information which will do the most good in a patient package insert in the absence of a national patient profile system is the requirement of regulating that

every prescription drug dispensed (except parenterals) must bear the generic name of the drug printed clearly on the direction label to the patient.

In addition, the public should be informed via television and radio advertising campaigns and through public service announcements (which may not cost the government anything except the make-up of the commercial announcement) that drug interactions cause many serious conditions and sometimes death. Patients should inform their doctor(s) of all the drugs—including vitamin and mineral supplements—they are taking, whether prescribed or purchased over-the-counter.

Types of Information to the Patient for Prescription Drug Labeling:

(1) On outside label (directions to patient) the generic name of the drug.

(2) Warning statement that drug interactions can cause adverse reactions or inhibit the beneficial effect of a drug and to read the prescription package insert carefully.

(3) An accurate list of the drugs and dietary factors which should not be taken while the patient is on this medication.

Experts should be invited to contribute authoritative drug interaction information and to serve on an advisory committee to the Food and Drug Administration for the purpose of the aforementioned compendium.

Individual drug firms should be asked to contribute copy toward a patient prescription package insert pertaining to the products they supply. The selection of drugs should be presently based upon those chemotherapeutic agents most widely prescribed and known to have adverse reactions or interactions with other widely prescribed drugs, common OTC products, and/or dietary factors. Eventually all drugs should be defined in like manner. **[The End]**

What's New on the Horizon?

By C. D. VAN HOUWELING

Dr. Van Houweling Is Director of the Bureau of Veterinary Medicine in the Food and Drug Administration.

WE IN THE BUREAU OF VETERINARY MEDICINE appreciate the chance to talk with representatives from other government agencies and industry as we confront the challenges facing all of us. In this connection, I am glad to see that the topic "What's on the Horizon?" does not contain the word—problems. I am reminded of what John Gardner said during one of his meetings with our Food and Drug Administration (FDA) staff. He said that when he became Secretary of Health, Education and Welfare (HEW), he soon recognized that the FDA faced many challenging opportunities that were being considered as insurmountable problems. I truly believe that this is the way we should look at what we too often call problems. They are, in fact, challenging opportunities, the kind of opportunities that make our jobs much more interesting, and require innovation and originality.

Food Shortage

This winter, I am sure that no one would disagree that all segments of the food-producing industry face some challenging opportunities. It is probably safe to say that at no other time in our memory has there been so much worldwide concern about the shortage of food. We are all vaguely uncomfortable with the knowledge that there are many millions of people in the world who are hungry, that many are starving, and that of those who survive many will be permanently impaired and unable to develop their full potential because of the malnutrition suffered early in their lifetime. This worldwide picture of hunger is quite a contrast to what we have in the United States. Food here at home—and especially some kinds of food—has become more expensive, but, compared to other parts

of the world, we are still very much in the land of plenty. As all of us who followed developments at the World Food Conference in Rome last month know, there is tremendous pressure on the "have" countries to share with the "have nots." I believe most of us are proud of the contributions that this nation has made over the years to feed and clothe people in less fortunate nations. However, it now becomes apparent, at least in some instances, that the gap between the "haves" and the "have nots" is even greater. More and more often the question is raised—Do we in the "have" nations possess the right to use so much of the world's food resources to feed only ourselves?

Plant v. Animal Protein

As far as the animal food industry is concerned, this food crisis raises a similar question—Can we continue to use the energy in food and fiber to feed animals? There is no doubt that the conversion of plant protein into animal protein requires additional food and energy and the availability of animal protein is a great plus for those nations which can afford to convert plant protein into animal protein for the nourishment of their people. In addition, we have become accustomed to eating an ample diet of animal protein. We would find a diet restricted exclusively to plant protein unappetizing, monotonous and generally not very satisfying.

The world food crisis should move all of us to dedicate ourselves anew to the most efficient production of food from animals we can achieve. This challenging opportunity comes at a time of shortages in feed ingredients, essential nutrients, and even in the ingredients needed to make drugs and feed additives. These shortages call for substitutes, and the ingenuity and innovation to find them. These substitutes also demand prompt action on the part of industry to propose their use, and on the part of regulating agencies—including the FDA—to act when substitutions can be made.

The Bureau has some prior experience with crisis substitutes. We are proud of our record in handling what has become known as energy crisis supplements. Insofar as I know, we have without fail, handled these supplements expeditiously and granted the approvals rapidly when the facts were presented to justify substitutions. Now, let's talk about something that might be called a feed crisis substitute.

Recycling Animal Wastes

As most of you know, the FDA has been involved for the past year or more in trying to develop a regulation which would provide

a legal basis for recycling animal wastes as feed ingredients. There appears to be a very large nutrient resource available in the waste of animals that has not been adequately utilized. One large integrated poultry operator has reported to me that broiler litter, properly processed, can be fed as a substitute for alfalfa hay to cows that are being wintered to produce calves. I have also been reliably informed that cage layer waste—again if properly treated and processed—can be substituted for soybean oil meal in the feed for fattening cattle. I don't have to explain to this audience that such nutrient resources should not be wasted.

Why has the Agency taken so long to propose a legal method for what appears to be a very useful source of animal nutrition? Basically the question is the same one we confront in almost everything we approve. What are the benefits and what are the risks or possible hazards? We have found it very difficult to write a food additive regulation for animal waste. As you can readily imagine there are many questions that can be raised in regard to the possibilities for contaminating animals and food products. The danger of bacteria can be eliminated through processing and treatment, but then all the possible dangers from drugs, pesticides and other contaminants surface and must be dealt with. Although the Agency has been striving mightily to prepare proposed regulations for animal-waste recycling, the regulations still have not been completed.

In addition to the total nutrients that are available from this source, it should be pointed out that there are certain trace elements in some of the animal wastes that could replace shortages that occur, for example, in phosphorous. Traces of phosphorous in poultry waste could be used to advantage in feeding poultry or swine.

Benefit/Risk Concept

This general subject leads us squarely into what I believe is one of the most challenging opportunities that we face. Clearly stated, the challenge is "How do we decide how much benefit we must have before we accept a certain amount of risk?" The subject of benefit/risk has been discussed at length. I think it is correct to say that this is not a question that a scientific-regulatory agency, such as the FDA, can be expected to answer. We can total up the possible or potential hazards. We can even, with your help, perhaps, total up the benefits that may accrue. However, a question we should not have to answer is "What constitutes an adequate balance of benefit

versus risk?" We believe this is a question that must be answered by the people through their elected representatives, and by businessmen through their association representatives. The number one area of concern in this regard is the significance of minute amounts of drug residues in food from animals that have been treated with or fed drugs and residues that are in the range of picograms or nanograms or one to one million or one to one billion.

Elaborating further on the benefit/risk concept, it is pertinent that objective procedures be developed that will, in effect, quantitate this ratio. We are and have been able to quantitate the benefits. This has been possible through our joint efforts to show that drugs and additives are efficacious through the use of well-designed studies. With respect to the quantitation of risk, the state of the art is not as well advanced. As many of you are aware, the Agency, through our efforts to develop standards for defining the required tissue assay sensitivity for carcinogenic animal drug residues, has in effect attempted to define the amount of risk that will accrue from the use of these animal drugs. We are currently developing a final order based on our proposal of 1973, taking into account suggestions received in the comments on the proposal. Again, this has not been an easy task. Since it is a pioneering effort, it is no surprise that it is not easy to formalize and verbalize the Agency's policy. To try to do so is certainly a challenging opportunity and one we hope you will all share in as we proceed.

The Food, Drug, and Cosmetic Act requires that we either make a determination that a drug is unsafe for use under the conditions of approval or that new evidence has been produced (since the application was first approved) that shows the drug is no longer safe for the conditions of use. These are very difficult decisions to make in the absence of applicable data. Our toxicologists are constantly, and properly, asking for appropriate data to make these decisions possible.

Equally difficult to determine, and perhaps even more so in some instances, is the amount of contamination in a feed necessary to make it unsafe. In addition to the safety for animals, we have to take into account safety of food from the animals and the knowledge that almost all animals tend to bio-accumulate these contaminants, especially the chlorinated hydrocarbons, thereby producing amounts in the tissues of food animals which present a possible human hazard.

We have learned in recent years that catastrophies can result from accidental contamination of feed. Our first exposure, some years ago, was to polychlorinated biphenyls (PCBs). After two serious PCB incidents, we had reports of chlordane contamination of feed, resulting in some sizable animal destructions. Within the past year we have seen the havoc that dieldrin can raise when it gets into broiler feed. Most tragic of all, perhaps, is the recent polybrominated biphenyl incident in Michigan where a feed manufacturer inadvertently put this chemical into animal feed. The losses that this one incident has caused have not been calculated, as far as I know; but I do know that it resulted in the destruction of thousands of cattle and swine, perhaps over a million chickens. What it has done to the livelihood of many farmers in that state is beyond description. Finding a way to avoid this type of contamination would solve one of the great challenges the feed industry faces today. Certainly, we at the Bureau accept the challenge to assist in any way we can, but the possibility of anyone testing all animal feed ingredients for contaminants such as pesticides or industrial chemicals is unrealistic.

Testing Feed Ingredients

Recently I had a telephone call from a trade association representative who demanded that we guarantee that a tragic accident such as the one in Michigan not occur again. I assured him that if he knew how we could guarantee prevention of such incidents, I would be glad to have his suggestion. Frankly, we have not been able to devise a plan which would prevent such accidents in the future. However, we certainly are going to do more in the way of testing feed ingredients for pesticides and chemicals. We are going to work with the feed ingredient producers on conducting more tests and giving assurances to feed manufacturers, but no one should operate under the illusion that such accidents cannot happen again.

Some of you who attended the recent joint meeting of the National Advisory Committees on Food and Veterinary Medicine will recall that there was some discussion at that meeting in regard to the possible blending or dilution of such contaminated feed with uncontaminated product in an effort to reach an acceptable level. This has long been contrary to the FDA tradition. However, the Agency has begun to give some consideration to the necessity of permitting some blending and dilution of a product when the original contamination was beyond the control of the person who owns the feed ingredient and where we know that by dilution with a free feed, a

level can be reached and if properly controlled, will not damage the animals or result in contamination of food.

Efficacy of Drugs

In the area of drugs, there are the interesting challenges that we face in making proper evaluations of the efficacy data that is required for us to conclude that a drug is effective. That is to quote the Act: "that there is substantial evidence upon which it can be reasonably concluded that a drug will have the effect it purports or is represented to have under the conditions of use for which it is prescribed, recommended, or suggested on the labeling." We have been through many discussions, prepared many guidelines and protocols covering combination drug uses and many other types of products. We have diligently tried to be reasonable and practical in our requirements. We know that the sponsors of new drug applications have not always agreed with our decisions in this regard, but we have tried to maintain an active dialogue with the firms and their representatives attempting to arrive at reasonable data requirements. I think we must continue to talk and work together in trying to refine these requirements so that our decisions properly reflect the needs of the consumers, the requirements of the Act, and adequately discharge our responsibility to the veterinarians and livestock producers of the nation.

I began this talk with some comments on the world food crisis. In the months ahead, as the reality of this crisis makes itself clearer to all of us, it will affect our decisions. In the same way that last year we concentrated on ways to cope with the energy shortage, this year the world food scarcity will have us considering new ways to conserve and increase what is perhaps this country's greatest natural and human resources—the land, the know-how and the desire to produce ever increasing quantities of food. With this in mind, I would like to quote from the memoirs of an American who lived at another time, not too long ago, when food shortages threatened following World War II: "There is enough in the world for everyone to have plenty to live on happily and to be at peace with his neighbors." These were the words of Harry Truman, the man who launched the Marshall Plan, our first great effort to aid hungry people in foreign lands. Let us hope that we mobilize and utilize our food-producing capabilities so that his prophecy is indeed shown to be correct. **[The End]**

A Discussion of Assay Sensitivity Methodology and Carcinogenic Potential

By GEORGE H. GASS

Dr. Gass Is Director of the Endocrinologic Pharmacology Research Laboratory and a Professor in the Physiology Department and School of Medicine at Southern Illinois University.

SINCE SOME KNOWN CARCINOGENS are essential for human life, it is proposed that the zero tolerance (no residue) terminology in the Delaney Clause be worded and/or interpreted to read: "a biological zero tolerance (no physically active residue) must be required for compounds administered to animals as food additives or animal drugs."

Current analytical techniques have sufficient sensitivity to detect residue levels of compounds that produce biological changes in body functions, yet our assay methods are capable of detecting residue levels of these same compounds in test animals that are far below the levels that produce these same biological changes.

It is essential both from a nutritional and an economic basis that feed additives and animal drugs be used in the production of meat animals. This will soon be impossible if the "chemical" zero tolerance of the Delaney Clause is not changed—or reinterpreted—to a "biological" zero tolerance.

Carcinogenicity of DES

The "chemical" zero tolerance interpretation had resulted in the elimination of such compounds as diethylstilbestrol (DES) from

the marketplace. This was done even though the following facts were known:

The lowest dose of DES that produces mammary cancer in the most susceptible animal species—the C3H mouse—required a minimum of 6.25ppb—and probably four times that amount. A C3H mouse eats 5g/30g body weight per day, equivalent to 1/6th of his body weight per day while man eats 2 kg/75kg body weight per day, equivalent to 1/37th his body weight per day.

To put this on the same basis as the C3H mouse, man would have to eat 12 kg/day.

BUT: Since it requires at least 6.25 ppb DES in mouse diet, and the highest found in United States Department of Agriculture (USDA) controlled studies was 0.5 ppb in liver, man would have to eat 150 kg (more than 330 pounds of liver) per day *every day* to get the same dose as the mouse. *And,* since the probable carcinogenic dose level is really 25 ppb in this C3H mouse to show increased tumor incidence, man would have to eat 1320 pounds of liver *every day*. Since average serving of liver is about 4 ounces (¼ pound), even an avid liver lover would have a margin of safety of 5280 times the amount of DES he would be expected to ingest under ideal conditions. Further, work by this investigator and A. B. Okey has shown that this frequency of tumor formation requires that the DES intake has to be continuous every day to get maximal tumor formation.

Using the best data available today, we know that there is probably at least a minimum 50 fold margin of safety even in the most sensitive assay animal yet used for mammary carcinogenesis, such as the C3H mouse, over the maximal DES residues found in liver from implanted beef animals. (Emphasis on most sensitive animal tool—the C3H mouse).

As we continue our investigations we note that well over one thousand compounds have been found to be cancer-producing and we are just scratching the surface. Our own work shows two probable recent additions.

VITAMIN D CARCINOGENICITY

	CONTROL	0.5	1.0	2.0	4.0	8.0 PPB
NO. TUMOR	6	13	16	13	7	2
NO. ANIMALS	55	59	61	52	40	7
PER CENT TUMORS	10.9	22	26.2	25	17.5	28.6
MEAN LATENT PERIOD (DAYS)	535	474	488	507	491	641

This is not included as a scare tactic, but strictly to introduce what scientists have known to be true—many substances that are essential to life if misused will produce cancer. As if this is not enough, the administration of butter fat—and probably all fats—are carcinogenic at the proper dose level.

POSSIBLE TUMOROGENIC EFFECT OF LIPIDS

Group	Fat Added To Diet %	No. Animals	No. Developing Tumors	No. Living At One & One Half Years	% With Tumor	Average Latent Period (Days)
1	0	21	0	21	0	
2	19.5	21	6	15	28.6	449
3	0*	15	5	10	33.3	462
4	19.5*	16	8	8	50.0	410

Therefore, this investigator and Dr. G. B. Marion proposed the following research that would produce the data that would justify a "biological" zero tolerance interpretation of the Delaney Clause:

(1) Establish a minimum biologically effective dose of DES.

(2) Establish a maximum no harmful effect dose and a minimum harmful effect dose.

(3) Establish a safety margin.

(4) Determine biological activity of DES metabolites, such as DES glucuronide.

* 250 ppb DES Added to Diet. This is the amount of DES found most effective in producing mammary carcinoma in C3H Mice in this laboratory.

The current concept of "zero tolerance" for feed additive residues in animal tissues is neither nutritionally nor economically defensible. Yet, this is the interpretation of the Delaney Clause required of federal agencies in regulating growth-promoting additives in livestock feeds.

Convinced that much more scientific information was needed concerning the use of hormones to stimulate growth in livestock, the 92nd Congress of the United States set aside $100,000.00 in the 1973 Agriculture Appropriation bill to initiate a study of hormonal residues in beef liver at Southern Illinois University. Unfortunately, the Office of Budget Management withheld these funds.

The Court of Appeals has reversed the action taken by the Food and Drug Administration (FDA) to ban the use of DES in livestock feeds, and it is back on the market. However, the use of growth-promoting hormones to stimulate growth and feed efficiency continues to be seriously challenged. Yet, there is *absolutely no evidence* to support the contention that the extremely low hormonal residues that have been found in a few of the livers of treated cattle and sheep are detrimental to human health. There is only a single study which found that a level under 25 parts per billion DES fed to highly cancer-prone C3H mice would significantly increase the incidence of mammary tumors.

Misinterpreted Data

Unfortunately, these data have been seriously misinterpreted. Indeed, evidence that estrogen may actually decrease the incidence of cancer in women was indicated by Burch and Boyd in 1970. They found that women on estrogen treatment who developed breast cancer did so *ten years later* in life than a comparable group of women who received no estrogen treatments.

Certainly, it is not realistic to condemn the use of hormonal growth-promoting substances for livestock when no evidence is available that indicates that low tissue residues are harmful to the consuming public.

Particularly when the following facts are known:

(1) Cancer has been induced in humans and animals only after treatment with massive doses.

(2) Many other substances, such as essential amino acids, have been implicated in tumor formation.

(3) Recently, high protein and high fat diets have been incriminated as tumorogenic.

(4) The amount of estrogens used in human medicine for birth control and the treatment of the distressing symptoms of the menopause greatly exceeds the amount a person might ingest by eating liver from cattle that had been treated with estrogens.

(5) Women normally secrete rather high levels of estrogens, particularly during pregnancy, when approximately 2,000 mg. are produced.

The amount of DES residue which have been detected in livers of treated animals would amount to an intake of less than 0.02 mg. per year if a person ate one pound of liver per week. Even in highly sensitive mice, this would be without consequence, since it is known that DES treatment must be *daily* in order to stimulate tumor formation (Okey and Gass, 1968).

(6) Estrogens, either natural or synthetic, are metabolized by the liver. It is known that more than 80 percent of the DES that is found in animal liver after treatment is in the form of DES conjugates. Absolutely nothing is known concerning the carcinogenicity of these compounds since no studies have been conducted on these metabolites.

Delaney Clause Needs Reinterpretation

It is essential that a new interpretation be made of the famous Delaney Clause which states that:

"No additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal . . ." ". . . Except that this proviso shall not apply with respect to the use of a substance as an ingredient of feed for animals which are raised for food production, if the secretary finds (i) that, under the conditions of use and feeding specified in proposed labeling and reasonably certain to be followed in practice, such additive *will not adversely affect the animals* for which such feed is intended, and (ii) that *no residue of the additive will be found* (by methods of examination prescribed or approved by the secretary. . .)"

The most significant aspect of this clause is the concept of zero tolerance. As previously stated, a number of substances that are essential for life have been found to be carcinogenic when administered at extremely high levels. Complete elimination of these compounds from the diet would result in death. Yet if residues of these substances can be identified in tissues after ingestion, it can be banned from use as a feed additive. Current analytical techniques make it possible to detect tissue residues as low as one part per trillion. Future techniques will permit detection of even lower levels. Any compound that is biologically active will leave some evidence of its activity. Therefore, few feed additives will be safe from market withdrawal by the FDA since residues would be traceable in animal tissues.

We must establish a safety level for each feed additive, a level which is effective and yet is perhaps 1/100 to 1/1000th of the amount that has been found to be harmful to human health. **[The End]**

Mantel-Bryan—Its Faults and Alternatives Available After Thirteen More Years of Experimentation

By DAVID S. SALSBURG

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PAUL LEVY, THE PROBABILISTIC, once said that prediction is very difficult, especially of the future. By "prediction," he meant the practice of extrapolating a mathematical model beyond the region of data for which it was constructed. Mathematical models are, of course, only convenient fictions with which we "smooth" out irregularities of data in order to "understand" something about cause and effect. We can be reasonably sure that our fiction is useful as long as there are observed values near the ones we wish to "predict." In fact, there are few statisticians who would hesitate to "predict" a value in a region around which and within which there are many observations.

However, the further you get from the observed data, the more the prediction is based upon the arbitrary choices of your model (for example, on the "smoothness" of your fiction) and the less it is based on hard experimental fact. For instance, figure (1)* shows a set of observed data points to which I have fit two models. One curves upward, the other has a negative curvature. Note that in the region of the observed data, both models "predict" values just as "close" to the observations. However, to the right of the observa-

* For figure (1), see page 122.

tions, they are in considerable disagreement. It is axiomatic that it is reckless to wander very far from one's data.

However, in 1961, Mantel and Bryan recognized that there was a need to be reckless. Faced with unavoidable contamination of the environment by small amounts of known carcinogens or with possible contamination by a carcinogen whose ambient level would be below that which can be assayed, they asked how one could use what was then known about carcinogenesis to predict a reasonable and still "virtually" safe level. They used what experimental information they had available thirteen years ago and suggested a mathematical model that tended to be a bound on all reasonable models, suggesting that we extrapolate on the basis of that model.

Mantel and Schniederman have since suggested that the Mantel-Bryan procedure is considerably better than the standard toxicology approach of finding a "no effect" dose among animals and then calling some fraction of that a "safe" dose for humans. The standard toxicological procedure encourages the experimenter, say Mantel and Schniederman, to do poor experiments, to use a small number of animals and low doses in order not to find evidence of carcinogenesis in a new compound. The Mantel-Bryan procedure, they claim, with its built-in conservatism, rewards the experimenter who uses a large number of animals at a high dose.

"Cheap Shot"

I wish that were true. Unfortunately, it would appear from its proposed uses, that the Mantel-Bryan procedure is a kind of "cheap shot." It offers a quick answer to the question, what is a "safe" dose? One can calculate Mantel-Bryan safe doses by using data drawn helter-skelter out of the literature and based on experiments whose purposes were far removed from this kind of "knowledge." I don't blame the legal and administrative people who are eager to use the procedure. It gives them solid answers in the midst of the squishy data that too often bedevil the whole question of carcinogenesis.

However, I contend that these seemingly solid answers are fakes. We seek, in the Mantel-Bryan procedure, to find a dose that will give us a ridiculously low probability of cancer. What do we mean by a low probability of cancer? What does one chance in 100,-

000,000 mean? Reasonable probabilities like 20 percent or 5 percent or even 1 percent can be interpreted within the context of the experiments from which we estimate them. There are a number of different philosophical meanings to probability, but like mathematical models in the midst of their observed data, these differences have no practical effect as long as we deal with probabilities of this order. When you get down to one in several million, the "frequentest" philosophy requires that you be able to observe hundreds of billions of experiments to give it meaning, and the philosophies of personal probability offer an untracked wilderness. No one who is used to the tools of statistics ever expects to deal with probabilities much below one in 500. Thus, I suggest that the first fault of the Mantel-Bryan procedure is that it produces an "answer" of no meaning.

Sequence of Experiments

In scientific investigation, we usually have an interplay between well-designed experiments with purposes specific to the problem at hand, the analysis of those experiments, and the design of further experiments to follow leads derived from the analysis. If we have a suspected carcinogen, then any attempt to estimate "safe" dose levels should be based on a sequence of experiments and analyses dealing with that specific agent and aimed at understanding its effects at low doses. This is not as hopeless as it might seem. In the last thirteen years, the investigation of chemical carcinogenesis has gone on with a vigor as great as any other in the scientific world. We know a lot more about carcinogenesis than was available to Mantel and Bryan in 1961. I would like to show you one example of how much we do know.

Let us abandon the attempt to determine doses associated with low probabilities of occurrence. As I noted before, the very meaning of this concept is vague. Instead, let us think of carcinogenesis as a process which takes place in all of us—if we live long enough or if we are exposed to a sufficiently high level of a carcinogen over a sufficiently long period of time. Then, we might define the safe dose of a carcinogen as one for which the probability of tumor before age 90 is less than 1 percent. That is, we might ask that we be 99 percent sure that any human being would have to be exposed to the agent for 90 years or more before coming down with a tumor. You

do not like 90 years? Try 120. Let society set the parameters that define "safety," but in this view those parameters will have more than metaphysical meaning.

For the past year, I have been engaged in an extensive review of the carcinogenic literature, and I have come to see that literature as a huge jigsaw puzzle on which small groups of people are working in different corners. There are over 50 journals in which significant work has been published and many in the field are ignorant of work published in journals outside their normal ken. I have had the advantage that I am not busy experimenting, so I can look around and see what these workers are doing and how their pieces of the puzzle fit into other pieces put together by other workers. I have found three large segments of the puzzle that appear to fit together with a remarkable ease. I have sent Mr. Mantel an advance copy of these remarks and some details of my mathematics, so he may want to comment.

Druckery Lines

Starting in 1943 but working mainly in the 1960's, H. Druckery of West Germany has been conducting a remarkable series of experiments on time-to-tumor as a function of dose for a number of known carcinogens. Out of these experiments, Druckery has derived a rough mathematical model which has come to be called Druckery Lines.

Of course, I am not alone in noting Druckery's work. Albert and Altshuler have attempted to use it to find an alternative approach to the Mantel-Bryan procedure. Schniederman quoted extensively from Druckery's major paper in a recent symposium. What I would like to point out is that Druckery's work fits very neatly with work done by Doll and published in 1971 in the *Journal of the Royal Statistical Society*.

Doll and Druckery are not unaware of each other's work. Doll was a participant in the 1967 symposium at which Druckery's results were most widely disseminated. At that time, Druckery also called attention to a tentative mathematical model proposed by Doll from human cancer registry data. What has been missing in this jigsaw puzzle is a more general realization of how close Druckery and Doll are to each other. In the 1971 paper, Doll made use of extensive tumor registry data from the United Kingdom and the United

States. He was able to derive an empirical probability function which fit that data. Schniederman quoted Doll's formula but failed to notice that Druckery's median time-to-tumor is implied by Doll's probability function. To test the other direction, I reconstructed Druckery's data for two carcinogens and found that Doll's probability function fits Druckery's data.

Functional Form

Thus, we have the same general functional form made to fit two entirely independent sets of data by two investigators, one of them dealing with animal experiments, the other dealing with human tumors.

Finally, there is a third piece to the puzzle that Druckery, Doll, Schniederman, and Altshuler have all missed. To put this third piece into perspective, let me describe a process that leads to the Doll-Druckery model. Each molecule of a carcinogen can be thought of as having a certain probability of striking a cell. The time needed to strike is a random variable, which may be infinite (no strike at all). If the strikes are independent of each other, then the Doll-Druckery model can occur if malignant tumors are caused by the last of a finite series of strikes. The number of strikes needed is a function of the carcinogen being used. The mean time to strike is a function of the dose (Druckery thinks it is a linear function; Doll suggests that it might be quadratic).

During the 1950's Shimkin did a number of experiments with urethane induced lung tumors in mice. His purpose was to perfect an assay that might enable him to investigate the nature of carcinogenesis. Whether he succeeded or not is of no matter here. But, in 1966, he brought his data to the prestigious Berkeley Symposium on Mathematical Statistics and Probability. There the world-renowned statistician Jerzy Neyman joined with Elizabeth Scott to analyze his data. They concluded that carcinogenesis is a single-hit multistage process. That is, a single molecule of the carcinogen modifies a cell, giving rise to two clones from the daughter cells. These clones have a death rate greater than their birth rate and so do not go on to tumor. A second molecule then strikes a cell in one of these clones, giving rise to two newly modified clones. These clones may or may not have death rates greater than their birth rates. If so, it takes another strike on a cell in one of these clones, and so on. Eventually,

after a finite number of strikes, one of the clones leads to a tumor. A sequence of independent random times to strike, such that cancer occurs only after the largest of a fixed number of them, is exactly what is needed for Doll's model.

Reasonable Bounds

So where are we in 1974 that we were not in 1961? We are now in the position to design rational experiments and estimate parameters of carcinogenesis for any specific compound. We can run experiments using doses large enough to produce tumors in short periods of time and still have some security in the applicability of those results to effects that would occur at very low doses and to humans. The Neyman-Scott-Doll-Druckery model offers us methods for putting conservative but reasonable bounds on the estimates of safety. It also gives us answers that make sense in terms of understandable consequences—time-to-tumor and intensity of dose either across time or in acute levels.

In addition, you cannot use the Neyman-Scott-Doll-Druckery model on a few numbers drawn helter-skelter out of the literature or produced incidentally out of experiments with another purpose. You must construct a group of well-designed and well-executed experiments for each suspected carcinogen. This, of course, is good science, and use of the Neyman-Scott-Doll-Druckery model achieves what Schniederman and Mantel hoped the Mantel-Bryan procedure would gain.

In a way, the projection of "safe" doses for carcinogens is a little like the early explorations of the Eastern coast of North America. Mantel and Bryan can be compared to Martin Frobisher who had the courage and the audacity to think the unthinkable, to probe those waters in the early years of the 16th century. He tried to settle colonies but failed because his colonies were secondary to the search for non-existent gold and the even more non-existent warm water passage to Asia. But it was Frobisher's maps of the coastline that led the way. Armed with those and the additional knowledge gained by the Spanish in more Southern water, Jacques Cartier was able to come back to those waters and explore the St. Laurence and the coast of New England with understanding. Like the French businessmen who supported Cartier, I hope you gentlemen can now put aside the intriguing charts of the earlier explorers with their promise of solution but their many false islands and vague terra incognita. The age of Cartier has come.

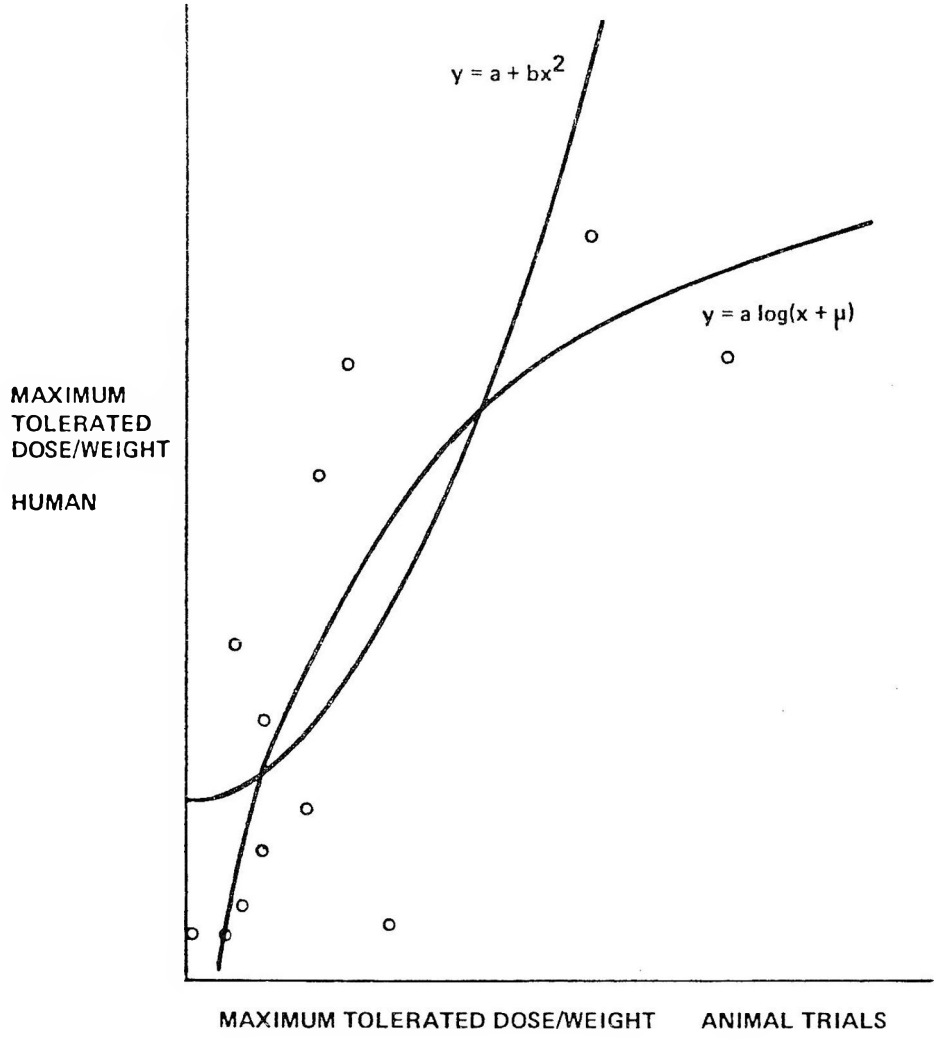
y = a + bx2
y = a log(x + μ)
MAXIMUM TOLERATED DOSE/WEIGHT
HUMAN
MAXIMUM TOLERATED DOSE/WEIGHT ANIMAL TRIALS

FIGURE 1

References

Albert, R. E. and Altshuler, B.: Considerations relating to the formulation of limits of unavoidable population exposures to environmental carcinogens in *Radionuclide Carcinogenesis,* Ballou, J. E., et al. (editors), AEC Symposium Series CONF-72050, NTIS, Springfield, Va., 233-253, 1973.

Doll, R.: The age distribution of cancer; implications for models of carcinogenesis (with discussion). *Journal of the Royal Statistical Society,* Series A, vol. 134, part 2, 133-166, 1971.

Druckery, H.: Quantitative aspects in chemical carcinogenesis in *Potential Carcinogenic Hazards from Drugs Evaluation of Risks in Treatment,* UICC monograph series, vol. 7, 60, Springer-Verlag, 1967.

Neyman, J. and Scott, E.: Statistical aspects of the problem of carcinogenesis. *Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability,* vol. IV., ed. Lecam and Neyman, 745-776, 1966.

Schniederman, M.: Safe dose? Problems of the statistician in the world of trans-science. *Journal of the Washington Academy of Sciences,* vol. 64, no. 2, 68-79, June, 1974.

[The End]

Biological Perspectives on Approaches to Sensitivity of Analytical Methods for Tissue Residues

By ROBERT G. ZIMBELMAN

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A PREVIOUS PRESENTATION (J. Ani. Sci., Supp. I)[1] described in detail an approach to making decisions regarding levels of hormones or other physiologically active agents which might occur as residues in tissues of treated animals. That presentation concerned itself with a definition of carcinogen, a basis for dose response with certain agents, the appropriateness of biological tests, and a decision-making proposal for animal models, including human studies whenever justified and feasible.

I do not intend to emphasize the importance of those aspects of my proposal but to make known perspectives that seem to be overlooked in the present effort of trying to establish a published procedure for the Food and Drug Administration (FDA) to use in its decision-making.

Taking a historical and philosophical overview on the use of statistical or mathematical procedures in various fields of biology leads me to some general conclusions. It appears that several fields of biological research have reached the point of scientific maturity, and use statistics in appropriate fashion. However, almost every field of biological research went through a phase in which there was resistance to statistical considerations by some scientists while others

[1] Zimbelman, R. G., Approach to Hormones as Drugs for Animals—Relationship to Delaney Amendment, J. Animal Sci., 38; Suppl. I, 68-76 (1974).

were eager to apply statistical techniques. In many fields, statistics or arbitrary mathematical formula approaches to handling the data eventually progressed to become an absolute *end point* of the scientific studies rather than a tool to aid in the interpretation of the biology involved. Further understanding of correct application of such procedures and an appreciation of misuse of such techniques eventually led to more appropriate utilization of statistics in the design and the analysis of biological experiments. I feel that it is justified to say that the field of toxicology, especially in regard to studies to determine a tolerance, may still be in the stage of accepting statistics as an end point—rather than as a tool for making biological decisions—and may be looking for arbitrary mathematical formula approaches as a solution to tough decision-making. I heartily support the application of appropriate statistical procedures in the design and the analysis of biological studies which relate to the determination of an acceptable level of residue for animal tissue. These techniques should provide recommendations on doses to be used, on the number of animals necessary, and on various other criteria, prior to beginning any given study. However, mathematical models which extrapolate beyond the data obtained and reach conclusions which ignore biological interpretations are of considerable concern to me.

Mathematical Model

In my opinion, the appropriate scientific studies which are interpreted biologically, with the aid of statistical analysis, should precede the application of any mathematical model to the results when establishing tolerance levels. A host of mathematical models have apparently been considered. It may very well be true that the use of any one or several of them is an improvement over the arbitrary judgments that have been made in the past. However, I propose that the *selection of any one model* to fit all chemicals is not a rational approach to decision-making. I can understand the motivation in having a mathematical model or technique which results in a very tangible value. Even if the answer is "wrong," a decision-maker can feel comfortable about it. Interpretation of biological results has never resulted in very tangible or universally accepted answers, since the statistical procedures provide probability estimates for certatin conclusions. Therefore, it is difficult to be comfortable with a decision based on biological interpretations which will be challenged. Nor can we ever expect biological interpretations to be as tangible or precise as a single value from the proposed mathematical techniques.

Rather than proposing strict adherence to one course or the other, it appears that a combination is useful in certain instances. I propose that the biological interpretations be made first, on the basis of appropriate statistical ansalysis. This will necessitate a decision as to whether or not any mathematical extrapolation formula procedure should be applied to the results. Also, if the interpretation is of such a nature that a decision is made to apply a mathematical extrapolation technique, then the mathematical technique whose assumptions best fit the particular scientific study should be the one applied.

"Cancer Seeds"

What is the basis for a decision as to whether to apply a mathematical extrapolation technique or not? A detailed description of this basis is in the publication previously mentioned. An analogy can be made by using plants instead of animals as an example. Plants are produced from seeds through a process of germination and growth, which results from the influence of modifying factors such as moisture, temperature and light. Seeds are directly responsible for plants while moisture, temperature or light only allow the seeds to become plants. Some chemicals may directly cause cancer ("cancer seeds") while others only allow for growth or expression of such "cancer seeds" which already exist in certain animals or animal models. I suggest that biological studies can be done to determine whether the chemical being studied is a "cancer seed" or simply modifies the expression of a tumor's potential in the animal model being studied. This expression may be reflected in an altered incidence of tumors at the same time interval in an animal's life or an altered time-to-occurrence of essentially the same incidence of tumors in control and treated animals. These end points (incidence or latency period) are of equal significance in making the first biological interpretation. Obviously, either "seeds" or "modifying factors" can be of concern to human health if humans are regularly exposed. I would propose, however, that there may be well-justified reluctance to accept dose-response considerations for "cancer seeds," but that dose-response considerations are very appropriate for modifying factors. This is especially true when the modifying factors are essentially identical in biological profile to substances normally produced in the body of both animals and humans. Once the biological interpretation described above has been made, then application of the mathematical extrapolation technique to chemicals which appear to be "cancer seeds" may well be the most defendable approach to setting a tolerance. However, the

present proposals may be so conservative that they prevent any use of compounds to which they are applied even if the benefit is great and the risk infinitesimally small.

Biological Effects

Some biological effects that suggest modifying factors do not fit the assumptions of presently proposed mathematical extrapolation techniques are given below.

(1) Many hormones will cause a *significant decrease* in tumor incidence or an *increased latency period* at low doses but an *increased incidence* or *decreased latency period* at certain higher doses. When doses which increase tumor incidence are only at or above those which mimic the normal physiological effects, the substance would not appear to be a "cancer seed." To the extent that animal models provide a basis for predicting human effects, then a reduced tumor incidence should be a basis for recommending a given level for daily consumption while other levels would be considered undesirable. Yet, application of the mathematical extrapolation technique, irrespective of these biological considerations, would provide an ultra-conservative estimate of a biologically insignificant amount. Amounts at or below those which actually resulted in less cancer in treated animals would be considered harmful.

(2) Substances which either prolong or decrease the life span of test animals could falsely appear to be either increasing or decreasing the normal occurrence of tumors if the study is terminated at a given time interval. If the change in life span is considered a physiological or toxicological consequence of higher doses of the chemical, then its independent effects on tumor incidence may be evaluated only when the animals are studied for their entire lifetime. Otherwise, the tumors may appear at an earlier chronological age but are in reality occurring with the same frequency at the same stage of the animal's normal aging process. Substances which are of a hormonal nature or otherwise effect normal physiological responses are known to either increase or decrease life span at high doses. Thus, the interpretation of results becomes difficult unless nearly all animals have died at their own time rather than all having been sacrificed at a given period of time.

(3) Certain substances can interact with normal (or subnormal, but adequate) diets to promote better health in treated animals. Such a situation may also allow a greater expression of existing "cancer seeds." With certain essential nutrients, such as vitamins, frank deficiencies and death would result from restriction to levels determined by mathematical extrapolation techniques.

Statistical Interpretation

Important to proper statistical interpretation on a biological basis are at least these factors:

(1) Overall incidence of tumors.

(2) Tumor occurrence.

(3) Age at time of death.

(4) Cause of death.

(5) Type of tumor.

(6) Effect of agent studied on normal physiological occurrences. (Relate these to known consequences from the scientific literature).

(7) Other information on mode of action of drug on tumor occurrence (either incidence or time).

When such information is available on an untreated sample of animals as well as on animals treated at varying levels, then we can begin to make biological interpretations leading to the decision of whether to use a mathematical extrapolation technique.

If the FDA scientists feel uncomfortable being solely responsible for such decisions, some new approach might be indicated for sharing such responsibility. An expert panel of scientists from various disciplines—such as toxicology, physiology, nutrition, endocrinology—and various sources—such as industry, government, universities—could be requested to review the studies and the proposed interpretation. The American Institute of Biological Sciences represents one source for recruitment of such assistance. **[The End]**

Cosmetic Ingredient Labeling— A Status Report

By HEINZ J. EIERMANN

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RULE-MAKING is not a simple process.

When I talked on cosmetic ingredient labeling at the 1973 cosmetic workshop, it never crossed my mind that this subject would still be an issue worthy of discussion at this meeting. Apparently, the differences in procedural philosophy and the logistical problems were greater than had been expected.

It has not been easy to resolve the outstanding issues on ingredient labeling. However, the Food and Drug Administration (FDA) and the industry have been working diligently on this project and have made significant progress. We seem to be seeing the light at the end of the tunnel.

After the many expressions of dissatisfaction, the revisions, and the various discussions among the agency, the Cosmetic, Toiletry and Fragance Association (CTFA) and others concerned with this regulation, you might wonder where we now stand with ingredient labeling. This status report is intended to bring you up to date.

Please keep in mind that I will not be paraphrasing the final order. The revised sections of this regulation will remain tentative until the rule-making process has been completed. The first step will be the publication in the *Federal Register* of the newly revised final order. It is expected that the revised regulation will satisfy the earlier objections and obviate the requests for hearing. If no further objections are raised on the disputed issues and the earlier objections

and requests for hearing are withdrawn, the regulation will become effective on the date stated in the order. If the revised order fails to accomplish these objectives, all will be for naught. We will then have to establish an effective date for the order of October 17, 1973 and hold a hearing on the outstanding issues. The effectiveness of the provisions to which objections were made would be stayed until after the hearing.

The following, then, is the current status of ingredient labeling:

Declaration of Ingredients

(1) *Declaration of ingredients in order of predominance.* With some exceptions, the ingredients must be declared in descending order of predominance. Fragrance or flavor ingredients may be listed as fragrance or flavor. If an ingredient is both, it must be listed as both.

You will have the option to declare the ingredients that are present at a concentration of one percent or less without respect to order of predominance after you have declared the other ingredients in descending order of predominance.

Your other alternative will be to declare first the ingredients other than color additives in descending order of predominance and, then, the color additives in random order.

Your third, and, most likely, the preferred alternate method of ingredient declaration will be to list, first, in descending order of predominance, the ingredients other than color additives that are present at a concentration greater than one percent; second, in random order, the ingredients other than color additives that are present at one per cent or less; and third, also in random order, all color additives.

Declaration of Color Additives

(2) *Declaration of color additives of shaded cosmetics.* As far as the 24 shades of lipstick are concerned, one ingredient declaration may serve the entire shade line, provided changes in the composition of the base formulation of individual shades do not upset that portion of the ingredient declaration.

When you use one ingredient declaration for the entire line of lipsticks, the composite ingredient declaration must list all color additives that are used in the 24 shade formulations.

You may, however, restrict an ingredient declaration to a limited number of shades, in which case the composite ingredient declaration

needs to list only the color additives that are contained in the shade formulations that the particular declaration encompasses. If the base formulation varies in composition from one shade to another, this change must, of course, be reflected in the respective ingredient declarations.

(3) *Declaration of color additives where a cosmetic product contains an assortment of cosmetics in the same package.* Should an eye make-up compact contain three shades of eye shadow but the surface area available for labeling, or the area of the principal display panel, fall within a yet-to-be-established size limitation, you may declare all ingredients in one ingredient declaration. First, you would list the base ingredients in the cumulative, descending order of predominance and then, in random order, the color additives.

When the surface area of the eye make-up exceeds the yet-to-be-established size limitation, you may declare the ingredients in the same manner as you declared the ingredients of the 24 shades of lipstick. You list, again, first the ingredients of the product base in descending order of predominance, and then you list all of the color additives in random order. If the base formulations differ sufficiently in composition to affect the declaration of ingredients, your product label must bear separate ingredient declarations with regard to the base ingredients but not with regard to the color additives.

Let us assume that the eye make-up compact contained two eye shadows, one eye liner, and one mascara. You are permitted to list the color additives of all items with a single, cumulative ingredients declaration. The base ingredients of the individual items must be declared separately in descending order of predominance. The base ingredients of your two eye shadows, however, may be listed in one ingredient declaration when the surface area of the eye make-up falls within the aforementioned size limitation.

(4) *Declaration of color additives that are sometimes added for color matching.* Paragraph (a)(3) of the tentative revised final order of July 26, 1974 remains unchanged. When you add D&C Blue #1 lake or D&C Yellow #5 lake to an occasional production batch in order to adjust the color of your lipstick, you are required to declare these color additives on the label. If you do not declare these additives and one of your product batches must be adjusted, the lipsticks made from that batch are considered misbranded.

Declaration of Incidental Ingredients

(5) *Declaration of incidental ingredients.* Incidental ingredients do not have to be declared. An incidental ingredient is a substance which is present in the cosmetic at an insignificant level and which has no technical or functional effect in the cosmetic. It may enter the cosmetic as an ingredient of another ingredient or it may be added as a processing aid.

When you prepare a shampoo with 40 parts of a sodium lauryl sulfate paste which contains 0.5 percent formaldehyde as a preservative, the formaldehyde has to be declared on the label. In this case, the shampoo would contain 0.2 percent formaldehyde, and this amount of formaldehyde would definitely serve as a preservative.

On the other hand, if a cream formulation contained only two percent of that sodium lauryl sulfate paste, formaldehyde would not have to be listed because formaldehyde would not be expected to have a functional effect.

In the case of processing aids, filter aid which is added to a cologne and is later removed need not be declared. When a small amount of palmitic acid is added to a deodorant stick batch in order to neutralize the free alkali content of eight percent sodium stearate, the palmitic acid does not have to be declared because sodium stearate contains the sodium salt of palmitic acid as an ingredient. If a small amount of acetic acid were added for the same purpose, it would not be necessary to declare the acetic acid because the small amount of sodium acetate that was formed would not be expected to have a technical or functional effect in the deodorant stick. However, if two percent polyethylene glycol 400 were added to that same batch in order to adjust the stick's consistency to specifications, that ingredient would have to be listed because it would have a functional effect.

Declaration of Alternative Ingredients

(6) *Declaration of alternative ingredients in the event of ingredient shortages.* When raw material shortages force you to substitute ingredients, you have several options for declaring the substitutes. You may declare each alternative ingredient immediately after the normally used ingredient, or you may list all substitutes together following the full declaration of the normally used ingredients. In the first instance, the label would read, for example, "Isopropyl Myristate or Palmitate," or it may state "Glycerin or Propylene Glycol or

Butylene Glycol." When the substitutes are grouped at the end of the declaration, the alternative ingredients must be identified by the preceding phrase "may also contain" and they must be listed in the cumulative order of predominance.

Substitute formulations, when actually used, may also be displayed on stickers, hang tags, tapes or package inserts provided they are clearly identified as substitutes. In the case of package inserts, the outside of the package must bear a statement informing the consumer that an insert with a substitute ingredient declaration is or may be enclosed.

Declaration of Exempt Ingredients

(7) *Declaration of ingredients exempted from public disclosure.* The regulation of October 17, 1973 provides that ingredients which the FDA has accepted in confidence in accordance with the established procedure need not be declared on the label. Instead of a declaration of identity, the phrase "and other ingredients" may be used at the end of the ingredient declaration.

No changes are contemplated in the basic concept of this provision. However, there will be an addendum to the provision concerning the placement of the phrase "and other ingredients." In addition, the procedure for the determination of confidentiality will be changed somewhat in accordance with the "Freedom of Information" regulation, which will be established soon.

Because the revised ingredient regulation will permit you to declare alternative ingredients, the provision concerning the phrase "and other ingredients" will state that this phrase must be placed at the end of the declaration of the normally used ingredients and before the declaration of alternative ingredients.

As far as the new procedure for the determination of confidentiality is concerned, any voluntary submission of information which is considered confidential will have to be preceded by a pre-submission of the data for review of the request for confidentiality. When the request is granted, the records will be accepted without disclosure of the information to the public. Should a confidentiality request be denied, the pre-submission may be withdrawn or it may be submitted as public information.

The decision following the review of the pre-submitted data will be the final Agency action on a confidentiality request. However, any

Agency decision may be taken to court for judicial review. When suit is brought within a specified time period, the FDA will not require that the disputed ingredient be disclosed on the label until a court decision has been rendered.

Of course, any records marked confidential which are currently on file with the Agency and which have not yet been reviewed will be treated as pre-submissions and may be withdrawn in the event confidentiality is denied. We have no intention of penalizing those who, in the spirit of prompt voluntary compliance, submitted their records without awaiting the promulgation of the "Freedom of Information" regulation.

Labeling Requirements

(8) *Off-package labeling of cosmetics held in tightly compartmented trays or racks.* Small-size cosmetics that are displayed for sale in tightly compartmented trays or racks may declare the ingredients off-package on padded sheets or leaflets that are attached to the display unit and are conspicuous to the purchaser. These cosmetics are usually too small for the label to bear a lengthy ingredient declaration, and tapes, hang tags or other attachments are bound to get tangled up in tight quarters.

Off-packaging ingredient labeling will be permitted also for small-size shaded cosmetics, such as lipsticks and small eye make-up products, which are held off-counter in drawers or cabinets. In this case, the padded sheets or leaflets with the ingredient declarations must be attached to a color chart or similar device which is prominently displayed.

The refills of cosmetics which are a party to off-package ingredient labeling must have the copies of the ingredient declarations attached to—or inside—the nested disposable cartons in which these refills are usually packaged for storage and shipment.

(9) *Declaration of ingredients in letters of 1/32 inch in size.* With some exceptions, the minimum letter size for ingredient labeling is 1/16 of an inch. The FDA proposed in the revised order that the letter size may be reduced to 1/32 of an inch in cases where the total area available for labeling is less than five square inches. The CTFA requested that the 1/32 inch letter size be permitted for cosmetics whose principal display panel is five square inches or less. This matter is still under study.

Effective Dates and Unchanged Provisions

(10) *Effective dates.* As far as the effective date is concerned, the order will have two effective dates: (1) Labels with ingredient declarations must be ordered within one year from the date the order is published, and (2) the new labels must be used in production within an additional six months. Where justified, the FDA will grant extensions beyond the eighteen months for the use of old labels in inventory.

The order will not specify when cosmetic products that are shipped in interstate commerce must bear ingredient declarations. The Fair Packaging and Labeling Act encourages the orderly disposal of packages that are in inventory when a regulation is promulgated under the authority of this Act. Consequently, all items that are in inventory at the time ingredient labeling becomes effective may be shipped to the trade, and containers with silk-screened, lithographed or otherwise permanently affixed labels may be used up in the manufacture of cosmetics.

(11) *Provisions that were not changed.* A few provisions of the order of October 17, 1973 remain unchanged. They are: (1) the declaration of ingredients where the cosmetic is also a drug; (2) the requirements for the prominence and conspicuousness of the declaration; and (3) the requirements for the identification of the cosmetic ingredients in the declaration. I am sure you are familiar with these provisions. Therefore, I will not discuss them.

Conclusion

Permit me to emphasize again that my discussion of some of the forthcoming changes in the requirements on ingredient labeling must not be construed as a detailed disclosure of the revised provisions of the new order. The purpose of my talk was to present a status report on ingredient labeling, encompassing the major changes that had been negotiated during the past year. Several issues are still unresolved, and some items may be modified within the framework of current accord by the time the regulation is published.

The tentative revised final order attracted 75 comments from consumers, the cosmetic industry and two trade organizations. The majority of comments were from small cosmetic manufacturers and distributors who felt that ingredient labeling would create serious economic hardships. Most requested that ingredient labeling be aban-

doned and suggested that the safety of the consumer be advanced by other regulatory means.

Although the FDA is greatly concerned about the economic impact of any of its orders on the regulated industry, it will always decide in favor of consumer safety when safety and economic impact are at cross-purposes. In the case of ingredient labeling, however, the primary purpose of the order is to prevent consumer deception and to facilitate value comparisons. Furthermore, the Agency is not convinced that implementation of this order will create an undue economic hardship.

The FDA advised the representatives of small cosmetic manufacturers in a recent meeting that repeal of the regulation was not an issue at this time. The representatives intimated that they may take the final order to court for judicial review. Therefore, it is possible that, even after publication of the revised final order, cosmetic ingredient labeling is still beyond our reach for some time to come.

[The End]

CONTROLS PROPOSED FOR VALIUM, LIBRIUM, AND RELATED DEPRESSANTS

All members of the benzodiazepine class of drugs, the depressants chlordiazepoxide (Librium), diazepam (Valium), clorazepate (Tranxene), oxazepam (Serax), flurazepam (Dalmane), and clonazepam (Clonopin) would be placed in Schedule IV of the Comprehensive Drug Abuse Prevention and Control Act of 1970 under a proposal issued by the Drug Enforcement Administration (DEA). The proposed DEA action is based on findings by the Assistant Secretary of Health, Department of Health, Education, and Welfare, and the Food and Drug Administration's Controlled Substances Advisory Committee, which reported that these drugs may lead to limited physical or psychological dependence. The proposal developed out of an initial review of chlordiazepoxide and diazepam; in line with the DEA's "class-action" approach to the evaluation of drugs for control, the review was expanded to include other members of the benzodiazepine class of drugs. Clonazepam, an unmarketed investigative drug, if its new drug application is given approval, will be controlled in Schedule IV at the time of marketing. Comments or objections to the proposal must be received by the DEA no later than March 28, 1975.

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