TOXICOLOGICAL EVALUATION OF MIGRATORY FOOD ADDITIVES*

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This month we observe the eighth anniversary of the enactment of the Food Additives Amendment. Many of you will remember the Congressional hearings prior to the enactment, the pleas of many that packaging materials should be covered by a separate law specifically drafted for indirect additives, the last minute debate on the Delaney Clause and some of the predictions of the effect of the law on industry and new product development.

Perhaps everyone was right, to a degree. The law was enacted, with a modified Delaney Clause, industry spent more time and money than anyone predicted, new product development and improvement have been delayed, and above all--food packaging should have been covered by a separate law specifically conceived and drafted for this complex group of materials.

However, eight years ago, we all accepted the fact that it was now the law of the land and that "any substance the intended use of which------may reasonably be expected to result, directly or indirectly, in its becoming a component----of any food" was a food additive and required approval of the Food and Drug Administration before use. Little did we realize what was in store for us, but we all put our best foot forward in an attempt to make the law work. I will not criticize anyone--except perhaps myself--because the motivation of everyone certainly was sincere. However, in our haste to comply, we proceeded without proper insight and knowledge of food packaging problems and are guilty of creating an unnecessarily complex maze of regulatory procedures.

Anyone who has the misfortune of trying to keep abreast of food packaging regulations realizes the complexity of our evolved system. The Lord's Prayer

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contains 56 words, the Ten Commandments 300 words, the Declaration of Independence 3,000 words. So far, our food packaging regulations contain over 43,000 words, about 10,000 words more than the regulations on all intentional food additives--for which the law was principally drafted.

Even a superficial examination of these regulations reveals that the vast majority of these words are devoted to the enumeration of thousands of chemicals for one or more specific uses under which most cannot migrate to food at an unsafe level regardless of their degree of toxicity. The one unanticipated result of this extensive cataloging of every chemical which remotely may come in contact with food, has been a growing apathy toward correct interpretation of the regulations. Unless you work with these regulations daily, are familiar with the multiple cross-references, and have sufficient technical training to understand what chemicals are covered by some of the vague generic terms, it is almost impossible to determine the approved uses of a given chemical. It is easy to understand why two manufacturers almost invariably will give conflicting statements about the food packaging status of the same product.

Above and beyond the problem of our inability to determine with certainty the status of a given chemical under the regulations, I am more concerned about the waste of our resources on matters which can be of no public health significance. Those of us in industry, government, or universities who apply our professional knowledge and judgment to problems in the field of environmental health have the moral responsibility to invest our limited resources in a manner which will give us the greatest return in terms of health protection. To silently and passively allow our energies to be diverted into predictably unprofitable research is beyond the dignity of any professional individual. Nevertheless, with each passing year there is more evidence of this type of research being conducted by myself and others. It would be tragic if history reports that our generation squandered its time and money on trivialities. Indeed, many of our investigations in the field of food packaging have fallen into this category.

Industry and government jointly are responsible for the current state of regulation of food packaging materials. In defense of us all, I must restate the fact that we had very few guidelines to serve as a basis for a more intelligent approach. However, in the eight years which have intervened, we have learned much and many of our previous assumptions are no longer valid or necessary. It is this experience which I wish to review today and to offer a modest start toward a major change in the scientific and regulatory approach to food packaging materials.

The basic procedure for the evaluation of safety of any food packaging material is very clearly and succinctly stated in the Food Additives Amendment [409(c)(5)], "the Secretary shall consider among other relevant factors:

(A) the probable consumption of the additive----------

(B) the cumulative effect of such additive in the diet of man or animals---------

(C) safety factors which in the opinion of experts---are generally recognized as appropriate for the use of animal experimentation data."

In actual practice, this means that it is necessary to know the probable consumption by man, the "no effect" level in experimental animals as determined by a two-year chronic toxicity study, and that a 100-fold margin of safety exists between these two.

The concept of the 100-fold margin of safety is generally recognized as a conservative approach to safety evaluation of food additives, and has been almost universally adopted in all developed countries. It is predicated on an assumption that the average human might be 10 times more susceptible to a given chemical agent than the most sensitive animal, and that some humans might be 10 times more susceptible than the average human, due to differences in body weight, food intake and habits, state of health, rate of metabolism, etc.

The 100-fold margin of safety frequently has been criticized as unduly conservative, but in the absence of direct human experimentation, it has served the profession well.

The first slide shows this relationship in its simplest form. If the probable consumption by man will be 0.01 ppm in the total diet, the minimum "no effect" level in experimental animals must be at least 1 ppm. Likewise, a consumption level of 0.1 ppm must be accompanied by a "no effect" level of 10 ppm, and so on.

Let me state the proposition a little differently. For a compound which becomes a component of man's diet at a level of 0.1 ppm, to be considered unsafe for this use, it would have to exert a toxic effect in experimental animals at a level of 10 ppm.

As I stated earlier, environmental health specialists have a professional responsibility to invest our resources in a manner which is most likely to protect or improve the health of the community. Therefore, I have attempted an analysis of the probability of detecting a potential health hazard from the use of a chemical of unknown toxicity which might be present in man's diet at any given concentration.

After considering several possible approaches to this analysis, I decided the most logical basis was to review as many of the two-year chronic toxicity studies as I could find and to tabulate the "no effect" level confirmed for each. I can make no claim that I have found every two-year chronic toxicity study which has been conducted. I can only claim that I have tabulated the "no effect" levels from every chronic study which I could find, without any selection or rejection. In total, I was able to locate two-year chronic toxicity studies on 143 different substances, and although this may seem like a modest number, it represents between 7 and 10 million dollars in toxicologic research. Undoubtedly, these 143 represent a large percentage of all such

studies which have been conducted and, I believe, constitute a representative cross-section.

Slide 2 provides a tabulation of the "no effect" levels for all of these 143 compounds. It is apparent from this tabulation that a small percentage of compounds will be extremely toxic---having a "no effect" level in experimental animals below 1 ppm, but that the majority will exhibit no toxic effect even at 100 ppm. Only 11 out of the 143 compounds demonstrated any toxic effect below 10 ppm. We might conclude that the odds of detecting a toxic effect at 10 ppm from an "unknown" compound are approximately 1 in 10.

Let us now look at this tabulation a little more closely and examine the nature of these 11 compounds which are toxic at 10 ppm or less. The next slide (3) shows the same information as the previous slide, except two additional columns have been added which subdivide these 143 compounds into two categories: 1) a heavy metals and pesticide category and 2) an all other category. I believe this breakdown is worthy of careful examination. The most apparent conclusion is that all 11 of the compounds, which were toxic below 10 ppm, were pesticides and heavy metals. I suspect every toxicologist could name these compounds with only a little reflection. Equally significant is the fact that 23 of the 24 compounds which were toxic below 100 ppm in experimental animals, were also pesticides or heavy metals. The only compound in the "other" category which was toxic below 100 ppm was acrylamide.

It is obvious that the degree of toxicity of pesticides and heavy metals (which were used as pesticides at one time) is quite different from that of other commercial chemicals. This should represent no surprise because pesticides are synthesized, screened and selected for their toxicity to one or more forms of life before becoming commercial products.

Therefore, if we exclude heavy metals and pesticides from our consideration, experience has indicated that only a very occasional

(approximately 1 out of 100) commercial compound will have a "no effect" level below 100 ppm and that an infinitely small number will exhibit any toxicity at 10 ppm or less.

Let us pause for a moment to consider whether this distribution of "no effect" levels is representative of commercial chemicals which might reach the consumer. Although 106 compounds may represent a large fraction of all the chronic oral toxicity studies ever conducted, they represent a very small fraction of all chemical compounds. It can be argued that those compounds which are selected for chronic toxicity studies may be less toxic than a completely random selection of chemicals from a handbook. Indeed, other highly toxic chemicals, besides pesticides and heavy metals, have been identified by the profession in acute and subacute inhalation and dermal studies in an attempt to establish safe levels of these materials in the work environment. However, these compounds are invariably highly reactive compounds which are used to synthesize other, more stable chemicals which become commercial products. Because of their reactivity, they could not be a component of a finished commerical product. This is especially true for food containers which by their very nature must be highly inert products and in their finished form must contain only components which are resistant to chemical change.

Consequently, within the self-limiting features of a component of food packaging, I believe the sampling is representative and justifies the following conclusion: Toxicological experience has indicated that, except for pesticides and heavy metals, any compound which might be used as a component of a finished food package or container, will be nontoxic to experimental animals at a dietary level of 10 ppm.

To express this conclusion slightly differently, I would like to show slide 4. This slide shows the probability of detecting an unsafe ingredient when expressed in terms of the probable consumption by man. In this slide the 100-fold margin of safety has been applied to the animal data

to express the corresponding safe level for man. It can be seen that at a consumption level of 0.1 ppm (corresponding to the 10 ppm level in the experimental diet) the probability of proving a compound to be unsafe approaches zero. Therefore, any component of a food package which contributes no more than 0.1 ppm to the human diet is generally recognized as safe, provided it is not a pesticide or heavy metal.

I invite your serious reflection on this conclusion. I have given it much thought and I sincerely believe it provides greater consumer protection than many of our widely accepted precepts.

Now let us for a few minutes consider the other aspect of the procedure for evaluating the safety of food packaging materials--the determination of the "probable consumption" by man. If we are to make any progress in our goal of investing our time and talent in projects which are most likely to give some return on the investment in terms of health protection, we desperately need some guidelines for calculating the consumption by man.

There is no doubt in my mind that Congress did not intend that everything which remotely may come in contact with food should be considered a component of food. Yet, this is precisely what we have done, and I place as much blame on industry for this situation, as on government. Most of this problem has been the direct result of our advances in analytical chemistry. Our extremely sensitive analytical methods have made it impossible to prove the lack of migration of almost any compound. Consequently, in the administration of our food laws, we have denied the existence of zero, because we can't prove it. To me this is analogous to denying the existence of night because we can't prove the absence of light. Obviously, we have not reached the degree of sophistication necessary to categorically say, "something is nothing!" and then forget about it. Realistically, at least for the time being, we must accept the concept that any compound which is used in a food container, or used in the manufacture of a food

container, may reasonably be expected to become a component of food even if only at a molecular concentration. This concept does not mean, however, that all of these uses involve any conceivable hazard to health, or that they require regulation under the law to assure their safe use. The question we continually ask ourselves is: "Which do not?"

Let us consider our concept that a food packaging component which contributes less than 0.1 ppm to the human diet is generally recognized as safe and evaluate our experiences on migration studies in an effort to determine which uses of packaging components will not exceed that level.

First of all, it is obvious to everyone, that any major component of a food container must be assumed to possess the capability of migrating to food at a biologically significant level, unless proven otherwise. It is to protect against this possibility that food packaging materials were included in the law. However, it is equally obvious to everyone, that at some level of addition, minor components cannot become a component of the diet at a level in excess of a generally recognized as safe concentration--0.1 ppm. Is that level 0.01%, 0.1%, or 1.0%?

I would like to assure you that this has not been an easy question to answer. I spent many a sleepless night trying to come to grips with the problem until I realized that I was still applying many of the uninformed assumptions which we made shortly after the Food Additives Amendment was passed.

At that time we were faced with compliance without any guidelines on industry practice. Toxicologists, like myself, who knew little about food packaging industry were given the assignment of investigating the safety of current industry practices. Guidance was essentially nonexistent because the food packaging industry is not a single entity, but a heterogeneous mixture of ~~adhesive~~ adhesive manufacturers, plastic and paper converters, can manufacturers, and

chemical suppliers, just to name a few. Each segment of the industry offered different advice on how to proceed, varying from petitioning for everything used by the industry to assuming everything was exempt.

In order to start the programs in the evaluation of safety of these materials it was necessary to make certain assumptions about industry practices and degree of migration. Because there were essentially no facts to serve as guidelines, the assumptions which were made were ultra-conservative.

In the beginning, in order to estimate the maximum possible contribution to the diet of man, we generally proceeded as follows: determine the maximum concentration at which an additive might be present in the container (which in the case of processing adjuvants was based on an assumption of 100% retention), assume that the entire diet of man would be in contact with that container, assume that this diet would be packaged in the smallest container giving the greatest "surface to food" ratio and finally assume 100% migration of the additive to the food. A few calculations by this method soon revealed that everything could be a significant migrant to food--even a compound which might be present in the container at 1 ppm.

The next step which many investigators followed was to determine the degree of migration. For the vast majority of packaging chemicals, specific and sensitive analytical methods were not available for detection in food, and, as an analytical expediency, simulated solvents were used--water, dilute acid and alkali, hexane, etc. The saving in analytical costs was significant, but such studies have given us very little useful information on the amount of an additive contributed to the diet of man. I even question whether the savings in analytical costs have not been offset by unnecessary toxicological and administrative expenses. As a net result of these studies we were able to prove that everything could be a migrant at significant levels.

As far as the other assumptions are concerned, we still are without reasonable guidelines which will permit us to calculate the "probable consumption of the additive". I would like to direct attention to this phrase "probable consumption of the additive", because this is a quote from the Food Additives Amendment, and this is the level which we and the Secretary of HEW are directed to consider--not the maximum possible consumption. And to determine this number, we still need many guidelines which are not available. Who can tell us what percent of the diet is exposed to uncoated paper or to plastic film? What fraction is dry, aqueous and fatty food? What is the average storage temperature and time? The average "surface-to-food ratio"? The same questions can be asked of each segment of the industry, adhesive, rubber, can manufacturers, and in each case quite different answers will be received.

In the absence of such fundamental yardsticks we are still assuming that every chemical which even fleetingly comes in contact with food is a food additive requiring proof of safety and regulation under the law.

As I mentioned a few moments ago, I have wrestled with this problem of trying to assign reasonable values to these various parameters. After many unsuccessful attempts, I decided to abandon this conventional approach which we developed for want of facts, and to look at the data which has been developed in recent years on "true" migration to food.

By "true" migration, I refer to a study, in which the packaging component is incorporated into the substrate at its maximum functional level, and exposed to food under ordinary or slightly exaggerated storage conditions, followed by analysis of the food to determine the level of migration of the component. This type of study is the only type which can give any reasonable information on the "probable consumption" by man.

In Hercules, we have synthesized several radioactive packaging components--starting with polypropylene and polyethylene, alkylketene dimer, polyamide

epichlorohydrin resin, several rosin esters and rosin size for the purpose of conducting migration studies. However, in order to find some basis for resolving the question, "what level of a packaging component would give less than 0.1 ppm to the diet of man?" I have selected the product which is most readily extracted from its substrate--rosin size. This material is an apt choice because it is not only readily soluble in fats and oils, but also possesses appreciable water solubility. I believe that rosin size is representative of the most readily migratable food packaging material. Moreover, paper, the substrate for rosin size, is well known to be the least resistant to penetration and extraction of all the packaging media. All of the technical facts argue that data from a study on the migration of rosin size from paper should represent a maximum for a component of any packaging media. Indeed, such data would be excessive for most uses of packaging components.

Let us now review the data on rosin size. All of these data have been published*, the details of which you can check at your leisure. As our first attempt at evaluating the level contributed to the diet, we used the typical simulated solvents. This was wasted effort, because in water and oil, the extraction was a direct function of time and temperature, and did not plateau until essentially 100% of the rosin size was extracted or the integrity of the paper sheet was destroyed. The impracticality of this approach was obvious. First of all, liquids are not packaged in uncoated paper and years of commercial experience with rosin sized paper had demonstrated it to be a suitable packaging material, with adequate shelf life. These extraction tests did confirm, for our purposes today, that rosin size on paper is an apt example of the extreme in tendency to migrate.

As a consequence of the failure of the simulated solvent test to help define the level of consumption, we prepared samples of radioactive rosin size, incorporated them into typical commercial paper and paperboard at known levels,

*R.W.Davison, L.R. Kangas, R.M. Miller and S.H. Watkins, "Migration of Rosin Components from Sized Paper to Exposed Foods", TAPPI Vol. 48, No. 8, August 1965.

packaged a wide variety of food in contact with these paper samples at typical package ratios, stored them at typical storage temperatures for typical storage times and determined the rosin size content of each food by counting the radioactivity.

The study was far more extensive than I will touch on today, because we used several types of paper (greaseproof, waxed, unwaxed, etc.), containing three different levels of rosin size, 24 different types of food (water, ice cream, oysters, apricots, green beans, wheaties, sugar, doughnuts, hamburger, butter, bacon, sausage, to name just a few) and analyzed each sample at several different storage intervals and temperatures. For our purposes today, I have selected only the uncoated and unwaxed paper and only the maximum ~~migration~~ migration levels obtained for the 18 commodities packaged in these uncoated papers under typical commercial storage conditions. Admittedly this gives unrealistic values for rosin size which are not typical of industry practice, but for our present purposes, the worst case must be presented.

Slides 5, 6, and 7 show the maximum migration value for 18 food commodities at various typical storage times and temperatures when exposed to paper containing an average of 4% rosin size. It is obvious from some of these values that high levels of migration can occur with some foods, whereas other foods contain much less rosin size. I am showing you these slides quickly since the individual values are of no great significance, but the composite of these values can be helpful. The next slide (8) shows the average consumption of these various commodity groups in the U.S.*, the average migration to that commodity group and a calculation of the probable level of rosin size in the total diet, if 100% of the diet were packaged in uncoated paper containing 4% rosin size.

* U.S. Department of Agriculture Dietary Evaluation of Food Used in Households in U.S. 1961

As I mentioned previously, three different sizing levels were used in these studies. The next slide (9) shows the final dietary calculations for the same foods, under the same conditions for paper containing 2% and 1% rosin size. The extrapolation is remarkably good. The last column shows the migration in ppm's expressed on the basis of a unit of 1% rosin size in the paper or container. For each percent addition to the container, if the entire diet of man was in contact with that container, his diet would contain 2 ppm of the additive.

Now I wish to carry this one step further to arrive at a realistic determination of the "probable consumption by man". Obviously, 100% of man's diet is not in contact with paper, or any other single type of food container. There are 5 major types of food container substrates, glass, metal, paper, plastic, and cellophane. It is impossible to get reliable figures revealing the percent of the food packaging market shared by each. However, it is conservative to assume that no more than 25% of man's diet is in contact with any given type of food package or packaging additive.

The next slide (10) shows a final calculation of the probable consumption by man which would result from the use of a component at a level of 1% in the container (as directly measured from the rosin size experiments) and the probable consumption from a level in the container of 0.2%. Undoubtedly, this calculation is an exaggeration for most uses of packaging components which possess greater insolubility or which are used in substrates more resistant to penetration than paper. Nevertheless, it permits the conservative conclusion shown on the next slide (11): "any component of an article contacting food which is present in the article or its coating at a level not exceeding 0.2% by weight is generally recognized as safe, provided it is not a heavy metal or pesticide".

I respectfully submit this conclusion to you. I do not contend that the wording is ideal from the legal or administrative point of view. However, I

believe it is scientifically sound and can be used as a basis for deleting the majority of the trivial citations in Subpart F of the regulations, and for eliminating much of the waste of time and effort being devoted to problems which can be of no possible public health significance.

To summarize these thoughts: toxicological experience has demonstrated that the vast majority of chemicals are nontoxic to experimental animals at 100 ppm in the total diet or higher. Except for pesticides and heavy metals, no compounds have been found to be toxic at less than 10 ppm. Applying the conventional 100-fold margin of safety, it is safe to assume that 0.1 ppm in the human diet would be safe for any chemical which would be a technically suitable component of a food container. Experience from migration studies have shown that a level of 0.2% by weight of a component of a food container will give less than 0.1 ppm to the human diet. Any component, of an article contacting food which is present in the article or its coating at a level not exceeding 0.2% by weight provided it is not a heavy metal or pesticide, is unworthy of any scientific or administrative attention and is generally recognized as safe.

SLIDE 1

GENERAL BASIS OF EVALUATION OF SAFETY OF FOOD ADDITIVES

Probable Consumption by Man	Minimum "No Effect" Level in Animals*
0.01 ppm	1 ppm
0.1 ppm	10 ppm
1.0 ppm	100 ppm
10.0 ppm	1000 ppm

* based on 2-year chronic experiments

SLIDE 2

DISTRIBUTION OF "NO EFFECT" LEVELS IN CHRONIC STUDIES

"No Effect" Levels, ppm	All Cpds. (143)
< 1	3
< 10	11
< 100	24
< 1,000	59
< 10,000	108

SLIDE 3

DISTRIBUTION OF "NO EFFECT" LEVELS IN CHRONIC STUDIES

"No Effect" Levels (ppm)	All Cpds. (143)	Hvy. Metals & Pesticides (37)	Others (106)
<1	3	3	0
<10	11	11	0
<100	24	23	1
<1,000	59	32	27
<10,000	108	37	71

SLIDE 4

PROBABILITY OF DETECTING HEALTH HAZARDS IN PACKAGING APPLICATIONS

Probable Consumption by Man	Probability of Proving Unsafe
0.01 ppm	→ 0
0.1 ppm	→ 0
1.0 ppm	1/100
10.0 ppm	30/100

SLIDE 5

MAXIMUM MIGRATION OF ROSIN SIZE FROM UNCOATED PAPER UNDER TYPICAL STORAGE CONDITIONS (4% ROSIN SIZE IN PAPER)

Food	Temp. (°F.)	Time (Days)	Migration (ppm)
Milk Prod.			
water	34°	14	5.9
ice cream	10°	28	0.3
Vegetable			
g. beans	34°	7	1.3
g. beans	72°	14	4.1
lettuce	34°	7	2.4
potatoes	72°	28	0.2

SLIDE 6

MAXIMUM MIGRATION OF ROSIN SIZE - CON'T 2

Food	Temp. (°F.)	Time (Days)	Migration (ppm)
Meats			
grd. beef	34°	5	8.7
chicken	34°	3	7.2
beefsteak	34°	7	4.9
sausage	34°	5	124.0
Fruits			
apricots	72°	28	0.1
apples	72°	28	1.2

SLIDE 7

MAXIMUM MIGRATION OF ROSIN SIZE - CON'T 3

Food	Temp. (°F.)	Time (Days)	Migration (ppm)
Grain Prod.			
Puffed Rice	72°	14	5.8
Wheaties	34°	28	7.0
Flour	72°	28	0.2
Doughnuts	72°	3	0.9
Others			
Sugar	72°	28	0.2
Butter	34°	14	32.8

SLIDE 8

CALCULATION OF MAXIMUM MIGRATION OF ROSIN SIZE TO TOTAL DIET (4% ROSIN SIZE IN PAPER)

Commodity Group	% of Diet	Av. Migration (ppm)	Contrib. to Total Diet (ppm)
Milk Prod.	31	3.1	1.0
Veget.	20	2.0	0.4
Meat	18	38.2	6.9
Fruits	13	0.5	0.1
Grain Prod.	10	3.5	0.4
Sugar	5	0.2	0.0
Butter, oils	3	32.8	0.9
			9.7 ppm

SLIDE 9

MAXIMUM MIGRATION OF ROSIN SIZE TO DIET

Level of Size in Paper	PPM	PPM/%
4%	9.7	2.4
2%	4.4	2.2
1%	1.9	1.9

SLIDE 10

CALCULATION OF PROBABLE CONSUMPTION BY MAN

Max. Diet in contact 25%
Max. Total Diet Migration 2 ppm/ea. %

Conc. in Package	Probable Consumption
1.0%	0.5 ppm
0.2%	0.1 ppm

SLIDE 11

GRAS

ANY COMPONENT OF AN ARTICLE CONTACTING FOOD WHICH IS PRESENT IN THE ARTICLE OR ITS COATING AT A LEVEL NOT EXCEEDING 0.2% BY WEIGHT IS GENERALLY RECOGNIZED AS SAFE, PROVIDED IT IS NOT A HEAVY METAL OR PESTICIDE.