

SCIENTIFIC BASIS FOR INTER-INDUSTRY PROPOSAL

The fundamental position of the scientific advisors to the Inter-Industry Committee on Indirect Food Additives is that government cannot protect the public from every conceivable hazard to health. Because of limitation of scientific manpower and the priority of other national programs potential health hazards must be assigned relative probability factors and available resources applied to those with highest potential return in health protection. The eleven years since enactment of the Food Additives Amendment and the millions of dollars spent on toxicology of food packaging materials have established that potential health hazard from food packaging materials is extremely remote and that a significantly reduced effort in this area would be in the best interest of public health.

Without exception, all non-government scientists who presented their views at the National Conference on Indirect Food Additives (February 13-14, 1968) felt that the current system of regulation of indirect additives was diverting scientific effort from more important health problems. A specific proposal to help alleviate this problem was outlined by one of those scientists, Dr. John P. Frawley, of Hercules Incorporated. The overwhelming majority of other scientists speaking at the National Conference endorsed Dr. Frawley's proposal. In brief, the derivation of Dr. Frawley's proposal can be summarized as follows:

- a) An examination of all available chronic toxicity studies (245 compounds) revealed that except for heavy metals and compounds developed because of their toxicity -- as pesticides, all compounds were safe to

experimental animals when fed for a lifetime at 40 ppm in the total diet. Applying unusually conservative margins of safety, it was concluded that a dietary level of 0.1 ppm of any chemical suitable for use in food packaging can be considered toxicologically insignificant for man.\*

- b) Any food packaging component which can be shown by suitable migration studies to contribute no more than 0.1 ppm to the diet of man should be considered non-migratory and exempt from regulatory control.
- c) Based on extensive migration studies using uncoated paper and actual food packaging conditions, it was demonstrated that if all food were packaged in the uncoated paper, use of an additive at a level of 0.05% by weight of the container or its coating could not contribute more than 0.1 ppm to the diet.
- d) Uncoated paper is the most permeable type of food packaging material and consequently its components are most susceptible to migration. Therefore, components of other types of containers will migrate less than those used in paper.
- e) No more than 25% of the human diet is in contact with any specific food packaging additive.
- f) Therefore, any food packaging component (except heavy metals and pesticides) used at a level of 0.2% or less by weight of the container or its food contact surface

\*Because the rat consumes from two to four times the amount of food per kilogram of body weight as man, this represents approximately a 1000-fold margin of safety.

can contribute no more than 0.1 ppm to the human diet and should be exempt from regulatory control.

All of the major industry representatives endorsed the above proposal at the time of the National Conference. The Inter-Industry Committee still endorses these proposals as being scientifically sound and safe for public health.

Since the time of the National Conference, additional evidence has been accumulated which supports the steps in the derivation of the proposal. These are presented below:

- a) The initial compilation of two-year chronic studies published by Dr. Frawley (Food & Cosmetic Toxicol. Vol. 5, 293, 1967) contained 220 compounds. Since then it has been extended to 252 compounds. Table 1 presents the 32 compounds and the "no effect" levels which have been added since Dr. Frawley's publication. All additions support Dr. Frawley's conclusion that any compound suitable for use in food packaging can be considered toxicologically insignificant at a level of 0.1 ppm in the diet.
- b) After the National Conference, the National Academy of Sciences, Food Protection Committee appointed an Ad Hoc Committee on Toxicological Insignificance. This Committee of scientists recommended a number of quantitative guidelines on insignificance, one of which was that "if a

chemical has been in commercial production for a substantial period, e.g. 5 years or more, without evidence of toxicological hazard incident to its production or use, if it is not a heavy metal or a compound of heavy metal, and if it is not intended for use because of its biological activity, it is consistent with sound toxicological judgment to conclude that a level of 0.1 ppm of the chemical in the diet of man is toxicologically insignificant". This level is the same level proposed by Dr. Frawley as the appropriate level of toxicological insignificance for food packaging components.

- c) Dr. Frawley's original extrapolation from maximum quantity migrating to food to maximum concentration in the container was based on rosin size migration to food from uncoated paper. Since that time, comparable data have been obtained for a plasticizer migrating from polyvinyl chloride film. These data are summarized in Table 2, and confirm the conclusion that the uncoated paper used in Dr. Frawley's calculation represents the extreme condition.
- d) In Dr. Frawley's extrapolation to the container, he made the "assumption" that no more than 25% of the diet would be in contact with any specific food packaging component. In an effort to obtain

a more quantitative measure of the maximum dietary percentage which might be in contact with a specific substrate type, a survey of food packaging practices was conducted in four supermarkets. The 106 food items which compose the basis of the U. S. Department of Agriculture survey of food consumption were tabulated with the type or types of food contact surface. These data are presented in Table 3.

The total for each category of container is presented. The grand total exceeds 100% because foods which are commonly packaged in two or more types of containers are listed under all appropriate types. The absolute maximum of the average diet which may be in contact with a specific substrate is 45% for all types of plastics and plastic coatings. Other categories were 34% for glass, 32% for paper, 23% for can, 10% for cellophane and 6% for metal foil. About 23% of the diet is bulk packaged or not in sufficient contact to be considered packaged.

With the unlikelihood that any individual would consistently choose one type of container over another for food offered in several types of containers, and with the improbability of any minor component of

food packages being universally used in all of a container type, Dr. Frawley's estimate of 25% is reasonable and conservative.\*

- e) The proposal to exempt from regulation components present in containers at 0.2% or less by weight of the container or its coating has been formally endorsed by at least 23 other scientists who addressed letters to the Hearing Clerk expressing their personal professional conclusions. Table 4 lists the names of the experts who have officially stated that this level of use of additions is generally recognized as safe.

It is apparent that the Food and Drug Administration is reluctant to establish a level of insignificance in the total diet, or in the food container.

Because of difficulty of enforcing a level in the total diet, the Committee agrees with the Food and Drug Administration proposal to establish a level of toxicological insignificance in the packaged food. However, starting with a level of 0.1 ppm in the diet which has been recommended by the National Academy of Sciences as insignificant, and using the conservative dietary exposure of 25%, an extrapolation to 0.4 ppm in specific foods is apparent as a level of exemption rather than 0.05 ppm as proposed by the Food

\*In other areas of safety evaluation, it is customary to make reasonable assumptions concerning human exposure. Uses of most pesticide tolerances would exceed the ADI if the tolerance level was assumed to be present on 100% of the agricultural commodity. Many direct food additives would exceed the ADI if used at the maximum level in all permitted foods. In the case of food packaging, it is even less likely that a single chemical will be used by all manufacturers of even one type of substrate, much less all types.

and Drug Administration. For practical reasons, a level of 0.5 ppm is proposed by the Inter-Industry Committee, in light of the fact that the original calculations by Frawley employed a 1000-fold margin of safety. This additional 10-fold margin of safety beyond the conventional 100-fold safety factor also allows for any possible exposure to a chemical from other environmental sources than food.

It is also the firm recommendation of the Inter-Industry Committee that a level of exemption be established in the food container and its food contact surface. Scientifically, this is the most readily enforced point of addition of a chemical and practically the most useful for industry and government. With the restrictions placed on such an exemption as contained in the preamble of the Food and Drug Administration proposal, the level of 0.2%, as proposed by Dr. Frawley and supported by the scientific community is eminently justified and supported.

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TABLE 1

ADDITIONAL NO-EFFECT LEVELS ESTABLISHED BY TWO-YEAR FEEDING STUDIES<sup>1</sup>

<u>Compound</u>	<u>No-Effe</u> <u>Level</u> <u>(ppm)</u>
Acetone peroxides treated flour <sup>1</sup>	347 <sup>a</sup>
Alkyl (C <sub>9</sub> -C <sub>15</sub> ) tolyl methyl trimethyl ammonium chloride (Hyamine 2389) <sup>2</sup>	200
Alkyldimethylbenzyl ammonium chloride (Roccal) <sup>3</sup>	1,200
Alkyldimethylbenzyl ammonium chloride (unspecified) <sup>4</sup>	< 630
Arsanilic acid <sup>5</sup>	1,000
2H-1-Benzopyron-2-one (Coumarin) <sup>6</sup>	1,000
Butoxy polyethylene polypropylene glycol (UCON 50 HB260) <sup>7</sup>	10,000
4-tert-Butyl-2-chlorophenyl methyl methylphosphoramidate (Ruelene) <sup>8</sup>	1*
Butyl stearate <sup>9</sup>	1,000
Chlorine (free in H <sub>2</sub> O) <sup>10</sup>	100
Dibutyl sebacate <sup>9</sup>	62,500
2,6-Dichlorobenzonitrile (Dichlobenil) <sup>11</sup>	100*
(3-[3,4-Dichlorophenyl]-1-methoxy-1-methylurea) (Linuron) <sup>12</sup>	125*
Diethyl carbonate <sup>13</sup>	3,000 <sup>b</sup>
Di-isobutyl phenoxy ethoxy ethyl dimethyl benzyl ammonium chloride (Hyamine 1622) <sup>2</sup>	200
3-Ethoxy-4-hydroxybenzaldehyde (Ethyl vanillin) <sup>6</sup>	20,000
4-Hydroxy-3-methoxybenzaldehyde (Vanillin)	20,000
Isosafrole <sup>6</sup>	< 1,000
6-Methyl-2H-1-benzopyran-2-one (6-Methylcoumarin) <sup>6</sup>	3,500
1,2-Methylenedioxy-4-allylbenzene (Safrole) <sup>6</sup>	< 100 <sup>T</sup>
1,2-Methylenedioxy-4-propylbenzene (Dihydrosafrole) <sup>6</sup>	< 1,000
Methyl ethyl cellulose <sup>14</sup>	10,000
Monochloroacetaldehyde 2,4-dinitrophenylhydrazone (Olin 1763) <sup>15</sup>	100*
Nonyl phenoxy polyethylene (9) glycol ether (Tergitol nonionic TP-9) <sup>7</sup>	2,700
Phenyldimethylurea <sup>16</sup>	1,250*
Polyalkylene glycol ether (Tergitol nonionic XD) <sup>7</sup>	2,700
Polyethylene glycol homolog, containing 90,000 ethoxyl groups terminated by hydroxyls (Polyox WSR301) <sup>7</sup>	50,000
Polyethylene polypropylene glycol (UNOC 75 H1400) <sup>7</sup>	10,000
Polyethylene polypropylene glycol (UNOC 25 H2005) <sup>7</sup>	2,000
Sodium arsenate <sup>17</sup>	255 (62.5 ppm As)
Sodium arsenite <sup>17</sup>	54 (31.25 ppm As)
Sodium 2-ethyl hexyl sulfate (Tergitol anionic 08) <sup>7</sup>	6,400

<sup>a</sup>Diet contained 77% flour treated with 0.045% acetone peroxides comprised of 85 to 95% 2,2 dihydroperoxy propane and 5 to 15% bis-(1,1-hydroperoxy-1,1'-methyl) diethyl peroxide

\*Pesticide

<sup>b</sup>3000 ppm concentration in drinking water

T-Tumors at higher levels

<sup>1</sup>Supplemental List to that published in Food & Cosmetic Toxicol. Vol. 5, 293-308 (1967)

TABLE 1 (CONTINUED)

REFERENCES

1. Food & Cosmetic Toxicol. Vol. 5, 309 (1967)
2. Soap & Chem. Specialties Vol. 30, 147 (1954)
3. J. Am. Pharm. Assn., Scientific Edition, Vol. 40, 263 (1951)
4. J. Am. Pharm. Assn., Scientific Edition, Vol. 37, 29 (1948)
5. Proc. 12th World's Poultry Congr., Sidney, Australia, 234 (1962)
6. Food & Cosmetic Toxicol. Vol. 5, 141 (1967)
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8. Food & Cosmetic Toxicol. Vol. 6, 185 (1968)
9. AMA Arch. Ind. Hyg. & Occup. Med. Vol. 7, 310 (1953)
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12. Food & Cosmetic Toxicol. Vol. 6, 171 (1968)
13. Arch. Tox. Vol. 22, 98 (1966)
14. Food & Cosmetic Toxicol. Vol. 6, 449 (1968)
15. Toxicol. & Appl. Pharmacol. Vol. 8, 472 (1966)
16. Allied Chemical Corporation, Unpublished Data
17. Toxicol. & Appl. Pharmacol. Vol. 10, 132 (1967)

TABLE 2

MAXIMUM MIGRATION OF ROSIN SIZE<sup>1</sup> AND 2-ETHYLHEXYL  
DIPHENYL PHOSPHATE<sup>2</sup> TO TOTAL DIET

Commodity Group <sup>3</sup>	Approx. % of Diet	Average Migration (ppm)		Contribution to Total Diet (ppm)	
		Rosin Size <sup>4</sup>	Santicizer 141 <sup>5</sup>	Rosin Size	Santicizer 141
Aqueous & Wet Foods	43	3.1	2.2	1.3	0.9
Fats, Oils	3	32.8	120	1.0	3.6
Dry Foods	39	2.1		0.8	
Meat, Poultry & Fish	15	36.2	60	<u>5.4</u>	<u>9.0</u>
			TOTAL	8.5	13.5

Rosin Size 2.1 ppm/%

Santicizer 141 0.5 ppm/%

1. Rosin Size - 4% in paper
2. 2-Ethylhexyl Diphenyl Phosphate - Santicizer 141 - 28% in PVC Film
3. Commodity Groups Taken From Table 3 and Consolidated
4. Food & Cosmetic Toxicol. Vol. 5, 293 (1967) and TAPPI Vol. 48, 433 (1965)
5. AMA Arch. Ind. Hyg. & Occup. Med. Vol. 8, 281 (1953)

TABLE 3

AVERAGE QUANTITY OF FOOD USED IN AMERICAN HOMES<sup>1</sup> AND TYPE OF PACKAGING SURFACE CONTACTING FOOD<sup>2</sup>

<u>Food Group and Major Items</u>	<u>Quantity per Week (lbs)</u>	<u>Percent of Diet</u>	<u>FOOD CONTACT SURFACE<sup>3</sup></u>						
			<u>None</u>	<u>Glass</u>	<u>Can</u>	<u>Plastic or Plastic Coating</u>	<u>Paper</u>	<u>Foil</u>	<u>Cellophane</u>
<b>Milk, Cream, Cheese, etc.</b>									
Fresh fluid milk	19.13	18.8		X		X			
Evaporated milk	0.62	0.6			X				
Non-fat dry milk	0.13	0.1		X				X	
Cream	0.32	0.3		X				X	
Frozen milk dessert	1.68	1.6				X		X	
Cottage cheese	0.48	0.5				X			
Other cheese	0.68	0.7		X		X			X
<b>Fats, Oils</b>									
Butter	0.42	0.4					X	X	
Margarine	0.80	0.8				X	X	X	
Lard	0.26	0.3			X		X		
Vegetable shortening	0.34	0.3			X				
Salad, cooking oil	0.36	0.4		X	X	X			
Salad dressing	0.53	0.5		X		X			
<b>Flour, Cereal</b>									
Flour	1.56	1.6					X		
Prepared flour mix	0.48	0.5					X		
Breakfast cereal	1.06	1.0					X	X	
Rice	0.44	0.4					X		X
Cornmeal, grits	0.61	0.6					X		
Macaroni, other pastas	0.42	0.4					X		X
Other cereal, pastas	0.11	0.1					X	X	
<b>Bakery Products</b>									
Bread	4.36	4.3				X			
Crackers	0.51	0.5					X		
Rolls	0.34	0.3				X	X		
Cake	0.47	0.5					X	X	
Pie	0.33	0.3					X	X	

Food Group and Major Items	Quantity per week (lbs)	Percent of Diet	FOOD CONTACT SURFACE <sup>3</sup>						
			None	Glass	Can	Plastic or Plastic Coating	Paper	Foil	Cellophane
<b>Bakery Products (Cont'd)</b>									
Cookies	0.89	0.9				X	X		
Coffee Cake	0.31	0.3					X	X	
Doughnuts & other	0.44	0.4				X	X		X
<b>Beef</b>									
Beef steaks	2.23	2.2				X	X		
Beef roasts	1.42	1.4				X	X		
Ground beef	1.34	1.3				X	X		
Other beef	0.43	0.4				X	X		
<b>Pork</b>									
Pork chops, hams, loins	1.25	1.2				X	X		
Sausage	0.34	0.3				X	X		
Smoked hams	0.79	0.8			X				
Bacon	0.80	0.8				X	X		
Other pork	0.42	0.4				X	X		
<b>Variety Meats</b>									
Veal	0.16	0.2				X	X		
Lamb	0.18	0.2				X	X		
Liver, brains, tongue, etc.	0.26	0.3				X	X		
Frankfurters	0.56	0.5				X	X		
Other lunch meats	0.86	0.8				X	X		X
<b>Poultry</b>									
Chicken	2.62	2.6				X	X		
Other poultry	0.19	0.2				X	X		
<b>Fish</b>									
Fresh fish	0.64	0.6	X						
Frozen fish	0.13	0.1			X		X		
Canned fish	0.28	0.3			X				
Shellfish	0.15	0.1					X		

<u>Food Group and Major Items</u>	<u>Quantity per Week (lbs)</u>	<u>Percent of Diet</u>	<u>FOOD CONTACT SURFACE<sup>3</sup></u>							
			<u>None</u>	<u>Glass</u>	<u>Can</u>	<u>Plastic or Plastic Coating</u>	<u>Paper</u>	<u>Foil</u>	<u>Cellophane</u>	
Eggs										
Fresh eggs	2.69	2.6	X							
Sugar and Sweets										
Sugar	2.33	2.3						X		
Sirups, molasses, etc.	0.40	0.4		X	X					
Jelly & jam	0.45	0.4		X						
Candy	0.52	0.5			X	X	X			X
Potatoes										
Fresh potatoes	4.82	4.7	X							
Canned potatoes	0.10	0.1			X					
Frozen potatoes	0.17	0.2					X			
Chips, sticks	0.22	0.2			X	X	X			X
Other	0.06	0.1				X	X			X
Fresh Vegetables <sup>4</sup>										
Dark green leafy	0.35	0.3	X							
Carrots, pumpkin, squash	0.56	0.5	X							
Tomatoes	1.09	1.1	X							
Cabbage	0.65	0.6	X							
Lettuce	1.30	1.3	X							
Corn	0.51	0.5	X							
Onions	0.82	0.8	X							
Beans	0.46	0.5	X							
Celery	0.33	0.3	X							
Cucumbers	0.30	0.3	X							
Other	0.96	0.9	X							
Fresh Fruits <sup>4</sup>										
Citrus	2.51	2.5	X							
Cantaloupe	0.37	0.4	X							
Apples	1.38	1.4	X							
Bananas	1.45	1.4	X							
Melons	1.28	1.3	X							

FOOD CONTACT SURFACE<sup>3</sup>

<u>Food Group and Major Items</u>	<u>Quantity per Week (lbs)</u>	<u>Percent of Diet</u>	<u>None</u>	<u>Glass</u>	<u>Can</u>	<u>Plastic or Plastic Coating</u>	<u>Paper</u>	<u>Foil</u>	<u>Cellophane</u>
<b>Fresh Fruits<sup>4</sup> (Cont'd)</b>									
Peaches	0.24	0.2	X						
Berries	0.51	0.5	X						
Other	0.45	0.5	X						
<b>Canned Vegetables &amp; Fruits</b>									
Vegetables	2.93	2.9			X				
Fruits	1.59	1.6			X				
<b>Frozen Vegetables &amp; Fruits</b>									
Vegetables	0.62	0.6				X	X		
Fruits	0.05	0.1		X		X	X		
<b>Juices</b>									
Canned vegetables	0.54	0.5			X				
Canned fruit	1.41	1.4			X				
Frozen fruit	0.42	0.4			X	X	X	X	
Fresh fruit	0.46	0.5		X		X			
<b>Dried Vegetables &amp; Fruits</b>									
Vegetables	0.37	0.4					X		
Fruit	0.10	0.1					X		X
<b>Beverages</b>									
Coffee	0.74	0.7		X	X		X		
Tea & cocoa	0.19	0.2		X	X		X	X	
Cola	3.06	3.0		X	X				
Fruit	0.91	0.9		X	X				
Ginger ale, seltzer & diet	1.12	1.1		X	X				
Fruit ade & punch	1.02	1.0		X	X				
Beer & ale	1.94	1.9		X	X				
Whisky, gin, rum, brandy	0.18	0.2		X					
Wine	0.12	0.1		X					

<u>Food Group and Major Items</u>	<u>Quantity per week (lbs)</u>	<u>Percent of Diet</u>	<u>None</u>	<u>Glass</u>	<u>Can</u>	<u>Plastic or Plastic Coating</u>	<u>Paper</u>	<u>Foil</u>	<u>Cellophane</u>
<b>Soups &amp; Other Mixtures</b>									
Soups, sauces, gravy	0.92	0.9		X	X			X	
Puddings, popsicles, etc.	0.85	0.8			X		X		
Baby foods	0.17	0.2		X	X		X		
<b>Nuts &amp; Condiments</b>									
Shelled nuts	0.09	0.1		X	X	X	X	X	X
Unshelled nuts	0.03	0.1	X						
Peanut butter	0.30	0.3		X		X			
Catsup & sauces	0.38	0.4		X	X	X			
Pickles, olives, relish	0.49	0.5		X	X				
Salt	0.29	0.3					X		
Vinegar & other	0.23	0.2		X					
<b>TOTAL</b>	<b>101.77</b>		<b>23%</b>	<b>34%</b>	<b>23%</b>	<b>45%</b>	<b>32%</b>	<b>6%</b>	<b>10%</b>

FOOTNOTES

1. Average Quantity of Food Used in American Homes derived from "Food Consumption of Households in the United States Spring 1965" U. S. Department of Agriculture HFCS 1965-1966 Report No. 1.
2. Packaging Surfaces Contacting Food based on 1969 practices observed in survey of supermarkets: Food Fair, Acme, Hearn's, Penn Fruit.
3. Many foods are occasionally packaged in every type of food contact surface. For example, sugar flavored with cinnamon is sometimes packaged in glass. Because of the insignificance of these uses, only the more common container surfaces have been listed.
4. For fresh fruits and fresh vegetables, some items, as onions or lettuce are sometimes packaged in plastic paper and all are carried home in paper bags. Because of the small surface or short duration of contact, these have been listed under "None"--meaning not in contact with any packaging surface.

TABLE 4

EXPERTS WHO ADDRESSED LETTERS TO THE HEARING CLERK  
DECLARING COMPONENTS OF FOOD PACKAGING USED AT A LEVEL  
OF 0.2% OR LESS AS GENERALLY RECOGNIZED AS SAFE

A. M. Ambrose, Ph.D.	Professor of Pharmacology Medical College of Virginia
Frank R. Blood, Ph.D.	Director, Division of Toxicology & Professor of Biochemistry Vanderbilt University Hospital
Joseph C. Calandra, Ph.D., M. D.	President Industrial Bio-Test Laboratories, Inc
Sal M. Cannavo	Senior Research Chemist L. A. Dreyfus Company
Charles P. Carpenter, Ph.D.	Administrative Fellow Mellon Institute
Steven Carson, Ph.D.	Vice-President Food and Drug Research Laboratories, Inc.
William B. Deichmann, Ph.D.	Professor of Pharmacology University of Miami
Daniel M. Dent	For the Scientific Staff The Borden Company
David W. Fassett, M. D.	Director, Laboratory of Industrial Medicine Eastman Kodak Company
Leon Golberg, D.Sc., Ph.D.	Research Professor of Pathology Albany Medical School
Richard L. Hall, Ph.D.	Director of Research and Development McCormick & Company, Inc.
William H. Hunt, Ph.D.	Toxicologist Monsanto Company
John H. Kay, Ph.D.	Director Lifestream Laboratories, Inc.
R. Emmet Kelly, M. D.	Medical Director Monsanto Company
M. L. Keplinger, Ph.D.	Toxicologist University of Miami
Donald D. McCollister	Manager, Plant Science and Animal Health Registrations The Dow Chemical Company

Bernard L. Oser, Ph.D.

President  
Food and Drug Research Laboratories, Inc.

James L. Ritchie

President  
American Paper Institute

Henry F. Smyth, Jr., Ph.D.

Advisory Fellow  
Mellon Institute

Andrew A. B. Swan, M.B.

Director, Industrial Hygiene Research Labs.  
Imperial Chemical Industries Limited

Joseph F. Treon, Ph.D.

Manager, Toxicology Division  
Atlas Chemical Industries

Carrol S. Weil

Senior Fellow  
Mellon Institute

Geoffrey Woodard, Ph.D.

President  
Woodard Research Corporation