SIXTH EDITION

PATTY'S TOXICOLOGY

VOLUME 5

EDITED BY

EULA BINGHAM

BARBARA COHRSSEN

WILEY

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Sixth Edition

Volume 5

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Editors

CONTRIBUTORS

Daniel Acosta Jr.,
Michael Attfield
Irene M. Baskerville-Abraham
C. Stuart Baxter
Eula Bingham
Jessie Callaghan
Vincent Castranova
Barbara Cohrssen
John Dement
Jennifer Dipper
Ronald F. Dodson
Candace L. Doepker
Michael L. Dourson
Brett James Green
Lynne T. Haber
Ali K. Hamade
Steven J. Hermansky
Renuka Kapoor
Michael J. Kosnett
Eileen Kuempel
Richard A. Lemen
Morton Lippmann
Chris M. Long
Andrew Maier
Robert J. McCunney
James A. Merchant
Celeste Monforton
Peter Morfeld
Henry J. Muranko
Richard W. Niemeier
Ann Parker
Tiina Reponen
Carol Rice
Kenneth D. Rosenman
Joan E. Strawson
Joel A. Tickner
Peter A. Valberg
Gregory Wagner
David Warshawsky
Alison Willis
Susan Woskie
Jagjit S. Yadav

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Contributors

Daniel Acosta Jr., Ph.D., Winkle College of Pharmacy, Academic Health Center, University of Cincinnati, Cincinnati, Ohio

Michael Attfield, Ph.D., NIOSH, Morgantown, West Virginia

Irene M. Baskerville-Abraham, Ph.D., Toxicology Excellence for Risk Assessment, Cincinnati, Ohio

C. Stuart Baxter, Ph.D., Kettering Laboratory, University of Cincinnati, Cincinnati, Ohio

Eula Bingham, Ph.D., Kettering Laboratory, University of Cincinnati, Cincinnati, Ohio

Jessie Callaghan, B.Sc., Canadian Centre for Occupational Health and Safety, Hamilton, Ontario, Canada

Vincent Castranova, Ph.D., NIOSH, Morgantown, West Virginia

Barbara Cohrssen, MS, CIH, Cohrssen Environmental, San Francisco, California

John Dement, Ph.D., Division of Occupational and Environmental Medicine, Department of Community and Family Medicine, Duke University Medical Center, Durham, North Carolina

Jennifer Dipper, B.Sc., Canadian Centre for Occupational Health and Safety, Hamilton, Ontario, Canada

Ronald F. Dodson, Ph.D., FCCP, FAHA, Dodson Environmental Consulting, Inc., Tyler, Texas

Candace L. Doepker, Ph.D., The J.M. Smucker Company, Cincinnati, Ohio

Michael L. Dourson, Ph.D., DABT, Toxicology Excellence for Risk Assessment, Cincinnati, Ohio

Brett James Green, Ph.D., NIOSH, Morgantown, West Virginia

Lynne T. Haber, Ph.D., DABT, Toxicology Excellence for Risk Assessment, Cincinnati, Ohio

Ali K. Hamade, Ph.D., DABT, Gradient Corporation, Cambridge, Massachusetts

Steven J. Hermansky, Pharm.D, Ph.D., DABT, ConAgra Foods, Inc., Omaha, Nebraska

Renuka Kapoor, Ph.D., University of Cincinnati College of Medicine, Department of Molecular Genetics, Biochemistry, and Microbiology, Cincinnati, Ohio

Michael J. Kosnett, MD, MPH, Colorado School of Public Health, Denver, Colorado

Eileen Kuempel, Ph.D., NIOSH, Morgantown, West Virginia

Richard A. Lemen, Ph.D., MSPH, Asst. Surgeon General (Retd.), Canton, Georgia

Morton Lippmann, Ph.D., New York University School of Medicine, Department of Environmental Medicine, Tuxedo, New York

Chris M. Long, ScD, Gradient Corporation, Cambridge, Massachusetts

Andrew Maier, Ph.D., CIH, DABT, Toxicology Excellence for Risk Assessment, Cincinnati, Ohio

Robert J. McCunney, MD, MPH, Massachusetts Institute of Technology, Environmental Health Sciences, Cambridge, Massachusetts

James A. Merchant, MD, DrPH, Department of Occupational and Environmental Health, University of Iowa, Iowa City, Iowa

Celeste Monforton, DrPH, MPH, The George Washington University, Washington, DC

Peter Morfeld, Ph.D., Institute for Occupational Epidemiology and Risk Assessment of Evonik Industries, Essen, Germany and Institute and Policlinic for Occupational Medicine, Environmental Medicine and Prevention Research of Cologne University, Germany

Henry J. Muranko, MPH, CIH, CSP, Muranko & Associates, Inc., Scottsdale, Arizona

Richard W. Niemeier, Ph.D., NIOSH, Cincinnati, Ohio

Ann Parker, BS, Toxicology Excellence for Risk Assessment, Cincinnati, Ohio

Tiina Reponen, Ph.D., Kettering Laboratory, University of Cincinnati, Cincinnati, Ohio

Carol Rice, Ph.D., CIH, Kettering Laboratory, University of Cincinnati, Cincinnati, Ohio

Kenneth D. Rosenman, MD, University of Michigan, East Lansing, Michigan

Joan E. Strawson, MS, MTSC, JD, McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario, Canada

Joel A. Tickner, ScD, Massachusetts Lowell, Lowell, Massachusetts

Peter A. Valberg, Ph.D., FATS, Gradient Corporation, Cambridge, Massachusetts

Gregory Wagner, MD, Mine Safety and Health Administration, Washington, DC

David Warshawsky, Ph.D., Kettering Laboratory, University of Cincinnati, Cincinnati, Ohio

Alison Willis, B.S., Toxicology Excellence for Risk Assessment, Cincinnati, Ohio

Susan Woskie, Ph.D., CIH, University of Massachusetts Lowell, Department of Work Environment, Lowell, Massachusetts

Jagjit S. Yadav, Ph.D., Kettering Laboratory, University of Cincinnati, Cincinnati, Ohio

Preface

In this Preface to the Sixth Edition, we acknowledge and note that it has been built on the work of previous editors. We especially need to note that Frank Patty's words in the Preface of the second edition are cogent:

> This book was planned as a ready, practical reference for persons interested in or responsible for safeguarding the health of others working with the chemical elements and compounds used in industry today. Although guidelines for selecting those chemical compounds of sufficient industrial importance for inclusion are not clearly drawn, those chemicals found in carload price lists seem to warrant first consideration.
>
> When available information is bountiful, an attempt has been made to limit the material presented to that of a practical nature, useful in recognizing, evaluating, controlling possible harmful exposures. Where the information is scanty, every fragment of significance, whether negative or positive, is offered the reader. The manufacturing chemist, who assumes responsibility for the safe use of his product in industry and who employs a competent staff to this end, as well as the large industry having competent industrial hygiene and medical staffs, are in strategic positions to recognize early and possibly harmful exposures in time to avoid any harmful effects by appropriate and timely action. Plant studies of individuals and their exposures regardless of whether or not the conditions caused recognized ill effects offer valuable experience. Information gleaned in this manner, though it may be fragmentary, is highly important when interpreted in terms of the practical health problem.

While we have not insisted that chemical selection be based on carload quantities, we have been most concerned about agents (chemical and physical) in the workplace that are toxicological concerns for workers. We have attempted to follow the guide as expressed by Frank Patty in 1962 regarding practical information.

This edition includes toxicological information on flavorings, metal working fluids, pharmaceuticals, and nanoparticles which were not previously covered, and reflects our concern with their technology and potential for adverse health effects in workers. It also continues to include the toxicology of physical and biological agents which were in the Fifth Edition. In the workplace of this new century, physical agents and human factors continue to be of concern as well as, nanotechnology. Traditionally, the agents or factors such as ergonomics, biorhythms, vibration, heat and cold stress were centered on how one measures them. Today, understanding the toxicology of these agents (factors) is of great importance because it can assist in the anticipation, recognition, evaluation and control of them. The mechanisms of actions and the assessment of the adverse health effects are as much a part of toxicology as dusts and heavy metals. As noted in Chapter 74 in Volume 5, the trend in toxicology is increasingly focused on molecular biology, mechanisms of action, and, molecular genetics.

The thinking and planning of this edition was a team effort by Barbara and Eula based on the framework that was established for the Fifth Edition by us and Charles H. Powell who died in September 1998. The three of us have had a long professional association with the Kettering Laboratory: Charles H. Powell received his ScD., Barbara Cohrssen received a MS, and Eula Bingham, has been a lifetime faculty member. Many of the authors were introduced to us through this relationship and association.

We are grateful for the help of our expert contributors, many of whom we have known for 10, 20 or 30 years, to complete this edition. The team effort was fostered between the current editors by many of the first contributors to Patty's such as Robert A. Kehoe, Francis F. Heyroth, William B. Deichmann, and Joseph Treon, all of whom were at the University of Cincinnati, Kettering Laboratory, sometime during their professional lives.

The authors have performed a difficult task in a short period of time for a publication that is as comprehensive as this one is. We want to thank Meghan Lobaugh whose assistance is greatly appreciated. We would like to express our deep appreciation and thanks to everyone who has helped us with this publication.

EULA BINGHAM, Ph.D

Kettering Laboratory, Cincinnati Ohio

BARBARA COHRSSEN, MS

San Francisco, California

USEFUL EQUIVALENTS AND CONVERSION FACTORS

1 kilometer = 0.6214 mile
1 meter = 3.281 feet
1 centimeter = 0.3937 inch
1 micrometer = 1/25,4000 inch = 40 microinches
= 10,000 Angstrom units
1 foot = 30.48 centimeters
1 inch = 25.40 millimeters
1 square kilometer = 0.3861 square mile (U.S.)
1 square foot = 0.0929 square meter
1 square inch = 6.452 square centimeters
1 square mile (U.S.) = 2,589,998 square meters
= 640 acres
1 acre = 43,560 square feet = 4047 square meters
1 cubic meter = 35.315 cubic feet
1 cubic centimeter = 0.0610 cubic inch
1 cubic foot = 28.32 liters = 0.0283 cubic meter
= 7.481 gallons (U.S.)
1 cubic inch = 16.39 cubic centimeters
1 U.S. gallon = 3,7853 liters = 231 cubic inches
= 0.13368 cubic foot
1 liter = 0.9081 quart (dry), 1.057 quarts
(U.S., liquid)
1 cubic foot of water = 62.43 pounds (4°C)
1 U.S. gallon of water = 8.345 pounds (4°C)
1 kilogram = 2.205 pounds

1 gram = 15.43 grains
1 pound = 453.59 grams
1 ounce (avoir.) = 28.35 grams
1 gram mole of a perfect gas ≈ 24.45 liters
(at 25°C and 760 mm Hg barometric pressure)
1 atmosphere = 14.7 pounds per square inch
1 foot of water pressure = 0.4335 pound per
square inch
1 inch of mercury pressure = 0.4912 pound per
square inch
1 dyne per square centimeter = 0.0021 pound per
square foot
1 gram-calorie = 0.00397 Btu
1 Btu = 778 foot-pounds
1 Btu per minute = 12.96 foot-pounds per second
1 hp = 0.707 Btu per second = 550 foot-pounds
per second
1 centimeter per second = 1.97 feet per minute
= 0.0224 mile per hour
1 footcandle = 1 lumen incident per square foot
= 10.764 lumens incident per square meter
1 grain per cubic foot = 2.29 grams per cubic meter
1 milligram per cubic meter = 0.000437 grain per
cubic foot

To convert degrees Celsius to degrees Fahrenheit: °C (9/5) + 32 = °F
To convert degrees Fahrenheit to degrees Celsius: (5/9) (°F − 32) = °C
For solutes in water: 1 mg/liter ≈ 1 ppm (by weight)
Atmospheric contamination: 1 mg/liter ≈ 1 oz/1000 cu ft (approx)
For gases or vapors in air at 25°C and 760 mm Hg pressure:
To convert mg/liter to ppm (by volume): mg/liter (24,450/mol. wt.) = ppm
To convert ppm to mg/liter: ppm (mol. wt./24,450) = mg/liter

CONVERSION TABLE FOR GASES AND VAPORS[a]

(Milligrams per liter to parts per million, and vice versa; 25°C and 760 mm Hg barometric pressure)

Molecular Weight	1 mg/liter ppm	1 ppm mg/liter	Molecular Weight	1 mg/liter ppm	1 ppm mg/liter	Molecular Weight	1 mg/liter ppm	1 ppm mg/liter
1	24,450	0.0000409	39	627	0.001595	77	318	0.00315
2	12,230	0.0000818	40	611	0.001636	78	313	0.00319
3	8,150	0.0001227	41	596	0.001677	79	309	0.00323
4	6,113	0.0001636	42	582	0.001718	80	306	0.00327
5	4,890	0.0002045	43	569	0.001759	81	302	0.00331
6	4,075	0.0002454	44	556	0.001800	82	298	0.00335
7	3,493	0.0002863	45	543	0.001840	83	295	0.00339
8	3,056	0.000327	46	532	0.001881	84	291	0.00344
9	2,717	0.000368	47	520	0.001922	85	288	0.00348
10	2,445	0.000409	48	509	0.001963	86	284	0.00352
11	2,223	0.000450	49	499	0.002004	87	281	0.00356
12	2,038	0.000491	50	489	0.002045	88	278	0.00360
13	1,881	0.000532	51	479	0.002086	89	275	0.00364
14	1,746	0.000573	52	470	0.002127	90	272	0.00368
15	1,630	0.000614	53	461	0.002168	91	269	0.00372
16	1,528	0.000654	54	453	0.002209	92	266	0.00376
17	1,438	0.000695	55	445	0.002250	93	263	0.00380
18	1,358	0.000736	56	437	0.002290	94	260	0.00384
19	1,287	0.000777	57	429	0.002331	95	257	0.00389
20	1,223	0.000818	58	422	0.002372	96	255	0.00393
21	1,164	0.000859	59	414	0.002413	97	252	0.00397
22	1,111	0.000900	60	408	0.002554	98	249.5	0.00401
23	1,063	0.000941	61	401	0.002495	99	247.0	0.00405
24	1,019	0.000982	62	394	0.00254	100	244.5	0.00409
25	978	0.001022	63	388	0.00258	101	242.1	0.00413
26	940	0.001063	64	382	0.00262	102	239.7	0.00417
27	906	0.001104	65	376	0.00266	103	237.4	0.00421
28	873	0.001145	66	370	0.00270	104	235.1	0.00425
29	843	0.001186	67	365	0.00274	105	232.9	0.00429
30	815	0.001227	68	360	0.00278	106	230.7	0.00434
31	789	0.001268	69	354	0.00282	107	228.5	0.00438
32	764	0.001309	70	349	0.00286	108	226.4	0.00442
33	741	0.001350	71	344	0.00290	109	224.3	0.00446
34	719	0.001391	72	340	0.00294	110	222.3	0.00450
35	699	0.001432	73	335	0.00299	111	220.3	0.00454
36	679	0.001472	74	330	0.00303	112	218.3	0.00458
37	661	0.001513	75	326	0.00307	113	216.4	0.00462
38	643	0.001554	76	322	0.00311	114	214.5	0.00466

CONVERSION TABLE FOR GASES AND VAPORS *(Continued)*

(Milligrams per liter to parts per million, and vice versa; 25°C and 760 mm Hg barometric pressure)

Molecular Weight	1 mg/liter ppm	1 ppm mg/liter	Molecular Weight	1 mg/liter ppm	1 ppm mg/liter	Molecular Weight	1 mg/liter ppm	1 ppm mg/liter
115	212.6	0.00470	153	159.8	0.00626	191	128.0	0.00781
116	210.8	0.00474	154	158.8	0.00630	192	127.3	0.00785
117	209.0	0.00479	155	157.7	0.00634	193	126.7	0.00789
118	207.2	0.00483	156	156.7	0.00638	194	126.0	0.00793
119	205.5	0.00487	157	155.7	0.00642	195	125.4	0.00798
120	203.8	0.00491	158	154.7	0.00646	196	124.7	0.00802
121	202.1	0.00495	159	153.7	0.00650	197	124.1	0.00806
122	200.4	0.00499	160	152.8	0.00654	198	123.5	0.00810
123	198.8	0.00503	161	151.9	0.00658	199	122.9	0.00814
124	197.2	0.00507	162	150.9	0.00663	120	122.3	0.00818
125	195.6	0.00511	163	150.0	0.00667	201	121.6	0.00822
126	194.0	0.00515	164	149.1	0.00671	202	121.0	0.00826
127	192.5	0.00519	165	148.2	0.00675	203	120.4	0.00830
128	191.0	0.00524	166	147.3	0.00679	204	119.9	0.00834
129	189.5	0.00528	167	146.4	0.00683	205	119.3	0.00838
130	188.1	0.00532	168	145.5	0.00687	206	118.7	0.00843
131	186.6	0.00536	169	144.7	0.00691	207	118.1	0.00847
132	185.2	0.00540	170	143.8	0.00695	208	117.5	0.00851
133	183.8	0.00544	171	143.0	0.00699	209	117.0	0.00855
134	182.5	0.00548	172	142.2	0.00703	210	116.4	0.00859
135	181.1	0.00552	173	141.3	0.00708	211	115.9	0.00863
136	179.8	0.00556	174	140.5	0.00712	212	115.3	0.00867
137	178.5	0.00560	175	139.7	0.00716	213	114.8	0.00871
138	177.2	0.00564	176	138.9	0.00720	214	114.3	0.00875
139	175.9	0.00569	177	138.1	0.00724	215	113.7	0.00879
140	174.6	0.00573	178	137.4	0.00728	216	113.2	0.00883
141	173.4	0.00577	179	136.6	0.00732	217	112.7	0.00888
142	172.2	0.00581	180	135.8	0.00736	218	112.2	0.00892
143	171.0	0.00585	181	135.1	0.00740	219	111.6	0.00896
144	169.8	0.00589	182	134.3	0.00744	220	111.1	0.00900
145	168.6	0.00593	183	133.6	0.00748	221	110.6	0.00904
146	167.5	0.00597	184	132.9	0.00753	222	110.1	0.00908
147	166.3	0.00601	185	132.2	0.00757	223	109.6	0.00912
148	165.2	0.00605	186	131.5	0.00761	224	109.2	0.00916
149	164.1	0.00609	187	130.7	0.00765	225	108.7	0.00920
150	163.0	0.00613	188	130.1	0.00769	226	108.2	0.00924
151	161.9	0.00618	189	129.4	0.00773	227	107.7	0.00928
152	160.9	0.00622	190	128.7	0.00777	228	107.2	0.00933

CONVERSION TABLE FOR GASES AND VAPORS (*Continued*)
(*Milligrams per liter to parts per million, and vice versa;
25°C and 760 mm Hg barometric pressure*)

Molecular Weight	1 mg/liter ppm	1 ppm mg/liter	Molecular Weight	1 mg/liter ppm	1 ppm mg/liter	Molecular Weight	1 mg/liter ppm	1 ppm mg/liter
229	106.8	0.00937	253	96.6	0.01035	227	88.3	0.01133
230	106.3	0.00941	254	96.3	0.01039	278	87.9	0.01137
231	105.8	0.00945	255	95.9	0.01043	279	87.6	0.01141
232	105.4	0.00949	256	95.5	0.01047	280	87.3	0.01145
233	104.9	0.00953	257	95.1	0.01051	281	87.0	0.01149
234	104.5	0.00957	258	94.8	0.01055	282	86.7	0.01153
235	104.0	0.00961	259	94.4	0.01059	283	86.4	0.01157
236	103.6	0.00965	260	94.0	0.01063	284	86.1	0.01162
237	103.2	0.00969	261	93.7	0.01067	285	85.8	0.01166
238	102.7	0.00973	262	93.3	0.01072	286	85.5	0.01170
239	102.3	0.00978	263	93.0	0.01076	287	85.2	0.01174
240	101.9	0.00982	264	92.6	0.01080	288	84.9	0.01178
241	101.5	0.00986	265	92.3	0.01084	289	84.6	0.01182
242	101.0	0.00990	266	91.9	0.01088	290	84.3	0.01186
243	100.6	0.00994	267	91.6	0.01092	291	84.0	0.01190
244	100.2	0.00998	268	91.2	0.01096	292	83.7	0.01194
245	99.8	0.01002	269	90.9	0.01100	293	83.4	0.01198
246	99.4	0.01006	270	90.6	0.01104	294	83.2	0.01202
247	99.0	0.01010	271	90.2	0.01108	295	82.9	0.01207
248	98.6	0.01014	272	89.9	0.01112	296	82.6	0.01211
249	98.2	0.01018	273	89.6	0.01117	297	82.3	0.01215
250	97.8	0.01022	274	89.2	0.01121	298	82.0	0.01219
251	97.4	0.01027	275	88.9	0.01125	299	81.8	0.01223
252	97.0	0.01031	276	88.6	0.01129	300	81.5	0.01227

[a] A. C. Fieldner, S. H. Katz, and S. P. Kinney, "Gas Masks for Gases Met in Fighting Fires," *U.S. Bureau of Mines, Technical Paper No. 248*, 1921.

PATTY'S TOXICOLOGY

Sixth Edition

Volume 5

Toxicological Issues
Inorganic Particulates
Dusts
Products of Biological Origin
Pathogens

Contents

Trends in Industrial Toxicology

Eula Bingham, Ph.D. and Barbara Cohrssen, MS, CIH

When the first edition of Patty's Toxicology and Industrial Hygiene was published, in 1948, Frank Patty stated that this publication is not a medical book nor is it intended for legal reference. Its primary purpose was to present toxicological information in simple, understandable terms in sufficient detail to be of some use to all persons interested in safeguarding the health and welfare of working people and in improving the working environment. The information in industrial toxicology that is produced by industry, government, or academia has changed greatly in emphasis and direction since the first edition of Patty's Industrial Hygiene and Toxicology and most certainly since the fifth edition of Patty's Toxicology, 10 years ago.

In the United States, the first recognition of occupational disease appeared in an essay by Benjamin McCready in 1835 (1), published by the Medical Society of New York. Illnesses including dermatoses were noted as well as long hours, poor ventilation, and child labor. Some of the illnesses were from chemical exposures and dust, but it should be noted that ergonomic and human performance concepts were raised in these early writings as well.

Recognition of the relationship between workplace chemical agents and disease (industrial toxicology) moved rapidly in Europe during the last part of the nineteenth century. This activity and recognition may have been stimulated in Germany by the passage of the Bismarck's Workingmen's Insurance Law in 1885, which set up an insurance into which both employers and employees contributed an amount of about 6% of total wages paid out. And for this, the workers obtained free medical care as well as some compensation.

After World War I, the United States wanted to become independent of chemicals that had been imported from Europe, such as aniline and pharmaceuticals (aspirin). As a result, the chemical industry developed in the United States. Fortunately, manpower and facilities used during the war for manufacture of munitions were available after 1918, and several companies decided to use both of them to get into the organic chemicals business. Because neither employers nor workers had any previous experience in making and handling organic chemicals, the effects of unanticipated toxicity were encountered. By the 1930s, three of the large chemical companies of the United States had established in-house laboratories of industrial toxicology. The companies were Dow, DuPont, and Union Carbide. The purpose of these laboratories was to provide management with sufficient information about the toxicity of new chemicals to enable management to make prudent business decisions.

The Walsh–Healy Public Contracts Act was passed in 1936 and required government contractors with federal contracts of 10,000 or greater to set standards for sanitation and safety. As a result of the Walsh–Healy Act, by 1938 there were enough government-affiliated personnel engaged in the practice of industrial hygiene at the federal, state, and local levels to make possible the formation of the American Conference of Governmental Industrial Hygienists (ACGIH). In 1939, the American Industrial Hygiene Association (AIHA) was founded. These societies sought to bring collective knowledge and skills together to achieve a sound basis for all to carry out their responsibilities for recognizing, evaluating, and controlling those hazards of the workplace that cause occupational illness and disability, or even discomfort and reduction in efficiency. Above all, they believed in the possibility of controlling hazards through reduction of exposures to an acceptable level.

Following World War II, there was a marked expansion of the organic chemicals industry, particularly in the fields of

Patty's Toxicology, Sixth Edition. Volume 5, Edited by Eula Bingham and Barbara Cohrssen.

organic pesticides, elastomers, and other synthetic polymers for use in textile fibers or plastic films. Food technology changed to meet increasing demands for food that kept well, was convenient to prepare, was attractively packaged, and looked, felt, and tasted good. Questions soon arose, however, about the safety of the new pesticides and food additives and in particular about the possible toxic effects from long-term low-level exposure.

By 1950, Congress was considering the necessity for amending the Food, Drug, and Cosmetic Act of 1938 to meet the changed conditions, and the Food and Drug Administration (FDA) had begun asking manufacturers to conduct "lifetime" exposure of at least one species, usually the rat, to establish "proof of safety" before making a new food additive or pesticide.

Publication of journals on industrial hygiene and toxicology in the United States began in 1923, with the publication of the *Journal of Industrial Hygiene and Toxicology*, edited by Philip Drinker, ScD. It was the official organ of the American Association of Physicians and Surgeons. In 1950, it was joined with occupational medicine to form *Archives of Industrial Hygiene and Occupational Medicine* (2).

When AIHA was formed in 1939, there already was a journal devoted to industrial hygiene. It was the *Journal of Industrial Medicine*, with a section on industrial hygiene. This particular journal was the predecessor to the *AIHA Journal*. Papers on industrial toxicology were accepted by these journals.

In 1961, the Society of Toxicology was founded by toxicologists in the AIHA. The driving force was the lack of recognition being given to toxicologists by pharmacologists. It is the first time that an American journal was dedicated to toxicology, and it was called *Toxicology and Applied Pharmacology*. The 50th anniversary special issue of the Society of Toxicology reveals, to a great extent, the transition of this organization as an offspring of the industrial toxicants and their impact on workers' health to a role now mainly in mechanistic toxicology. However, two of the SOT areas in this special issue that are particularly relevant to industrial toxicology have gained recognition since the last edition of Patty's Toxicology—nanotechnology and endocrine disruption. Chapters on these areas are included in this edition.

The Food Additives Amendment of 1958 required that any new intentional or unintentional food additive have FDA approval, usually in the form of a regulation, published in the Federal Register as a response to the manufacturer's petition for the proposed use, before the material could be marketed. The need for toxicological information about chemicals is reflected in state and federal laws that were passed since 1950 to protect workers and consumers from chemical toxicity.

Carcinogenesis remains of great importance in industrial toxicology, and some of the most relevant research in epidemiology that remains today as "industrial or workplace toxicology" is found in the *American Journal of Industrial Medicine*. The toxicology to identify carcinogens in the industrial environment remains based on human studies and experimental studies. The second method of obtaining knowledge of the toxic effect of chemicals on humans is indirect. The substances are administered to animals and the results are extrapolated to humans. The development of short-term tests and toxicological mechanisms of action are now used by industry and governments to determine the severity of the hazard. The International Agency for Research on Cancer (IARC) indicates that mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity may be of sufficient importance to affect the overall evaluation for carcinogenicity (3). Direct observation of toxic effects on humans still occurs through the discipline of epidemiology.

One of the more significant events in industrial toxicology has been the closure of or drastic reduction in the size of industrial toxicology laboratories, especially in those companies and industries that led the way in developing the toxicological data during the 1950s to 1990s. If one were to examine the early editions of Patty's Toxicology, one would find that most of the chapters had been written by toxicologists doing the research at DuPont, Dow, Eastman Kodak, and Union Carbide. Those authors included Fassett, Gerarde, Hazelton, Hine, Kehoe, Irish, Patty, Rowe, and Stokinger, among others, whose names are well known in the development of industrial toxicological data upon which many current permissible occupational health standards are based.

In the past, it was these industrial toxicology laboratories that were researching the toxicological effects of chemicals on animals and looking at epidemiology data gathered by their in-house health departments and generating data. Now most of the research is being done in university toxicology laboratories, which are looking at the "mechanism of action" of a few or specific "interesting" chemicals; in other words, the biological mechanism of how the chemical is affecting the body or organism rather than a resultant health effect. And, these studies are usually funded by a governmental agency, such as the National Institutes of Health (NIH).

There are a few exceptions to this recent development in toxicological research: dioxins, flavorings (in particular, diacetal, the butter flavor), benzene, metal working fluids, and the effects of nanoparticles. These agents are the subjects of chapters not previously found in earlier editions. In the fifth edition, we added the toxicology of physical agents to the Toxicology volumes. These chapters have been updated to reflect the interest in mobile phone technology, the increased use of lasers, and the effects of shift work on safety in various professions.

Today, the National Toxicology Program (NTP) (4) provides a significant portion of all new data on industrial chemicals used in the United States and in other countries.

At present, 80,000 chemicals are used in the United States and an estimated 2000 new ones are introduced annually to be used in products such as foods, personal care products, prescription drugs, household cleaners, and lawn care products. The effects of many of these chemicals on human health are unknown, yet people may be exposed to them during their manufacture, distribution, use, and disposal or as pollutants in our air, water, or soil.

The National Toxicology Program was established by the Department of Health and Human Services (DHHS) in 1978 and charged with coordinating toxicological testing programs within the Public Health Service of the Department, strengthening the science base in toxicology, and providing information about potentially toxic chemicals to health regulatory and research agencies, scientific and medical communities, and the public. The NTP is an interagency program whose mission is to evaluate agents of public health concern by developing and applying the tools of modern toxicology and molecular biology. In carrying out its mission, the NTP has several goals:

- to provide toxicological evaluations of substances of public health concern;
- to develop and validate improved (sensitive, specific, rapid) testing methods;
- to develop approaches and generate data to strengthen the science base for risk assessment; and
- to communicate with all stakeholders, including government, industry, academia, the environmental community, and the public.

Nationally, the NTP rodent bioassay is recognized as the standard for identifying carcinogenic agents. However, the NTP has expanded its scope beyond cancer to include examining the impact of chemicals on noncancer toxicities such as those affecting reproduction and development, inhalation, and the immune, respiratory, and nervous systems. Recently, a Center for Evaluation of Risks to Human Reproduction and a Center for the Evaluation of Alternative Toxicological Methods were created.

NTP's testing program seeks to use mechanism-based toxicology studies to enhance the traditional approaches. Molecular biology tools are used to characterize interactions of chemicals with critical target genes. Examples of mechanism-based toxicology include identification of receptor-mediated toxicants, molecular screening strategies, use of transgenic animal models, and the development of alternative or complementary *in vivo* tests to use with rodent bioassays. Inclusion of such strategies can provide insight into the molecular and biological events associated with a chemical's toxic effect and provide mechanistic information that is useful in assessing human risk. Such information can also lead to the development of more specific and sensitive (and often less expensive) tests for use in risk assessment. There is a strong linkage between mechanism-based toxicology and the development of more biologically based risk assessment models. Such models are useful in clarifying dose–response relationships, making species comparisons, and identifying sources of interindividual variability.

The NIEHS Environmental Genome Project is a multicenter effort to identify systematically the alleles of 200 or more environmental disease susceptibility genes in the U.S. population. Information from this human exposure assessment initiative together with the environmental genome project will provide the science base essential for future, meaningful studies of gene–environment interactions in disease etiology (4).

As a part of an interagency human exposure assessment initiative, the NTP and the NCEH/CDC are collaborating on a pilot project to quantify approximately 70 chemicals in either human blood or urine that are considered endocrine disrupters. Biological samples from the National Health and Nutrition Examination Surveys (NHANES) are being tested. These data will be used to estimate human exposure to endocrine disrupting agents within the U.S. population and to identify those of greatest public health concern. This information can be used in prioritizing chemicals for study and in developing biologically based models for estimating human risks.

The revolution in genetics and specifically in mapping the human genome, as well as the development of transgenic animals, will radically change the way we evaluate chemical and physical agents.

Mixtures have reemerged as a special concern in toxicology. Mainly during the period (1930–1970) when complex mixtures, particularly those derived from fossil fuels (petroleum fractions, coal tar), were being actively investigated, the issues revolved around finding the critical chemical in the complex mix that was responsible for its toxicology. Chemicals in these mixtures enhanced or inhibited the critical chemical. When chemical exposures occurred either together or in sequence as in chemical carcinogenesis, the concepts of initiation and promotion became part of understanding mixtures. With this edition, we address in separate chapters, in this volume, the health effects from various energy sources (coal, petroleum) and their by-products.

The workplaces of concern in earlier editions of Patty's were mainly those in U.S. factories where chemicals and certain processes occurred. Today, many of those activities and chemicals have moved overseas, particularly to Asia, and the scene is dynamic and changing as we write. Asia is now the site of these new challenges. Hopefully, the toxicological information contained in these volumes will be useful in these and other global workplaces. We have welcomed authors from outside the United States, many of whom are