

THE 1989 TO 1990 TRYPTOPHAN RECALL

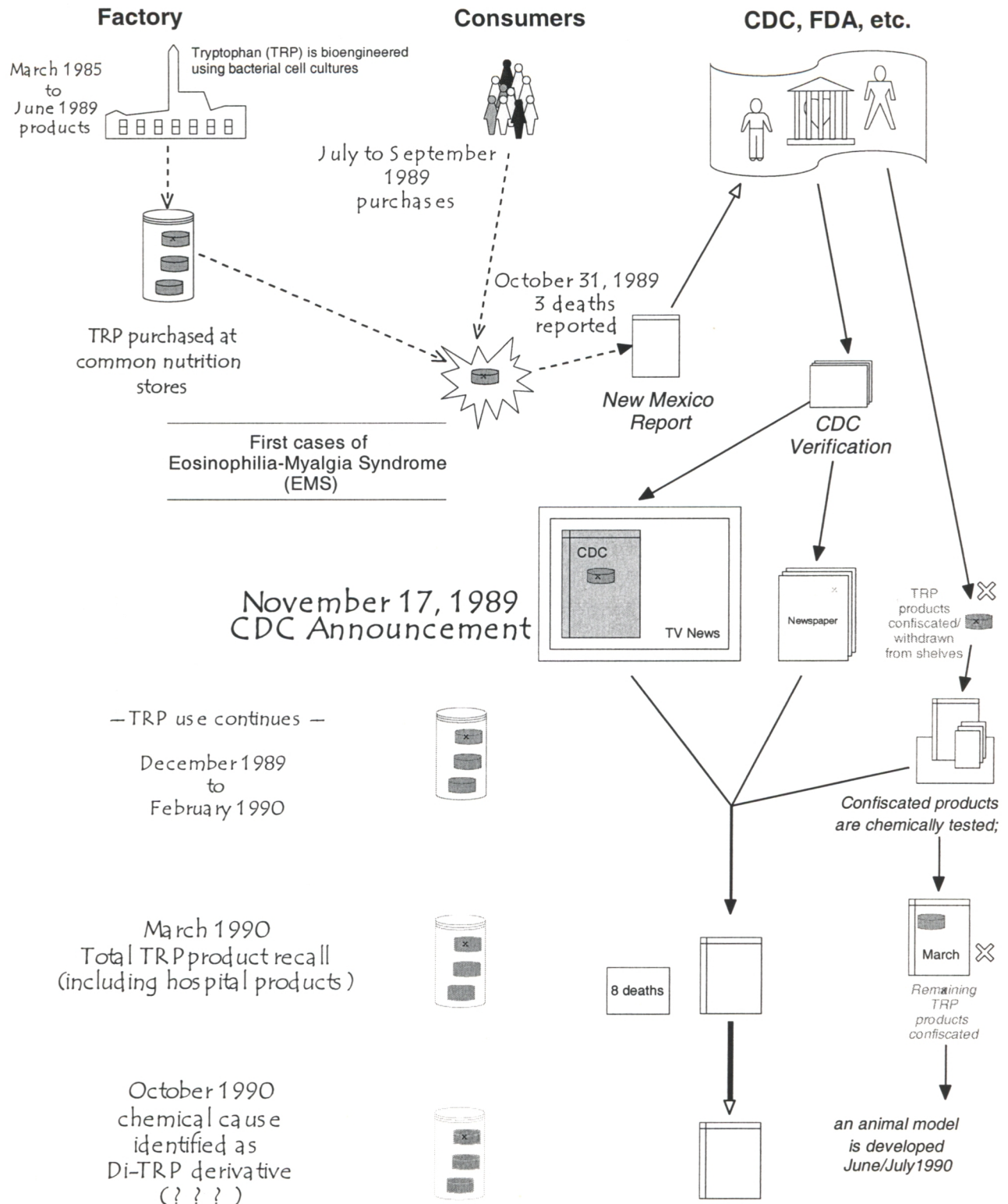


Table 5. 1992 U.S. Fermentation Products Market

Product	Sales, \$ × 10 ⁶
ethanol	1900
antibiotics	
bacitracin	65
cephalosporins	2340
penicillins	810
tetracyclines	590
others	1135
<i>total antibiotics</i>	<i>4940</i>
amino acids	
L-aspartic acid	16
L-lysine	215
MSG	60
L-phenylalanine	95
others	65
<i>total amino acids</i>	<i>451</i>
enzymes	
amylases	58
dextrinases	13
glucose isomerase	84
pectinases	12
rennin	11
others	25
<i>total enzymes</i>	<i>203</i>
organic acids	
citric	365
gluconic	43
lactic	22
others	19
<i>total organic acids</i>	<i>449</i>
miscellaneous	
fine chemicals	10
flavors and fragrances	20
steroids	15
polysaccharides	465
vitamins	7
<i>Total</i>	<i>8454</i>

Table 4. Worldwide 1992 Production and Sale Price for Fermentation Products^a

Product	Production, ^b t/yr	Sale price, ^b \$/kg
bacitracin	10,000	7.80 ^{c,d}
citric acid	325,000	0.8–1.25
erythromycin	3,000	52.00
gluconic acid	44,000	5.50 ^e
L-lysine	44,000	2.50 ^f
DL-leucine		75.00
monosodium glutamate	470,000	1.90
neomycin sulfate		90.00 ^g
L-phenylalanine	12,000	20.00 ^h
penicillin ⁱ	44,000	50.00
riboflavin (vitamin B ₂)		58.00 ^j
streptomycin sulfate		150.00 ^g
tetracycline HCl	15,000	55.00
L-threonine	10,000	13.08 ^j
L-tryptophan	4,000	68.00
vitamin B ₁₂	18	8,000 ^d
xanthan		6.00
pure brewer's yeast		2.40

^aChina, the world's largest producer of antibiotics, had a volume that exceeded 10,000 t in 1991 (25).

^bValues are estimates.

^cPrice per 10⁶ units.

^dUSP grade, nonsterile.

^eUSP grade, calcium salt.

^fMonoHCl, feed grade.

^gUSP grade.

^hEstimated production cost. Majority is used to make aspartame.

ⁱPotassium salt of benzyl and phenoxymethylpenicillin.

^jFeed grade.

Generally, for most fermentation processes to yield a good quality product at a competitive price, at least six key criteria must be met. (1) Fermentation is a capital intensive business and investment must be minimized. (2) The raw materials should be as cheap as possible. (3) Only the highest yielding strains should be used. (4) Recovery and purification should be as rapid and as simple as possible. (5) Automation should be employed to minimize labor usage. (6) The process must be designed to minimize waste production and efficiently use all utilities (26,27).

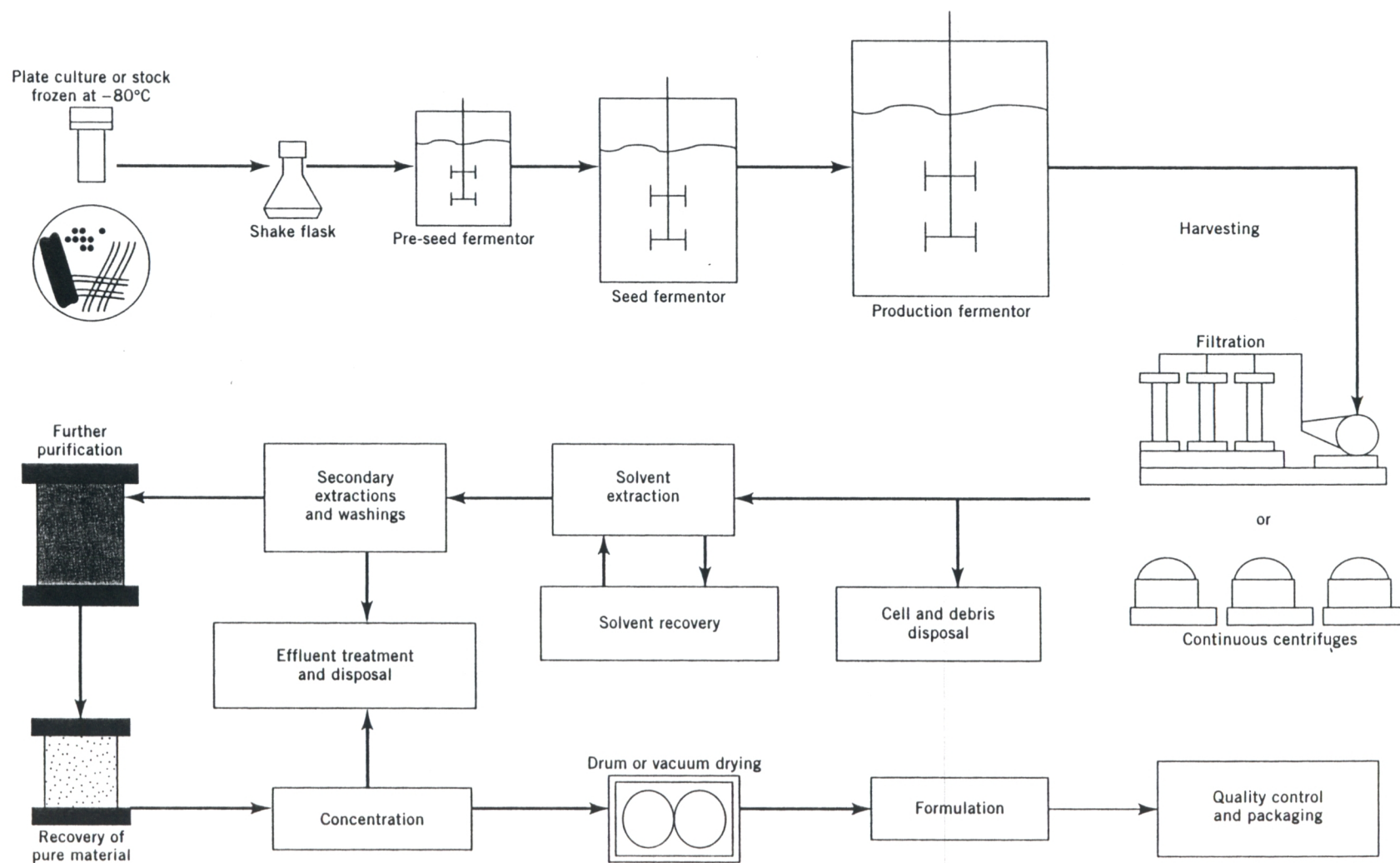


Fig. 2. Schematic representation of a fermentation process for an extracellular product.

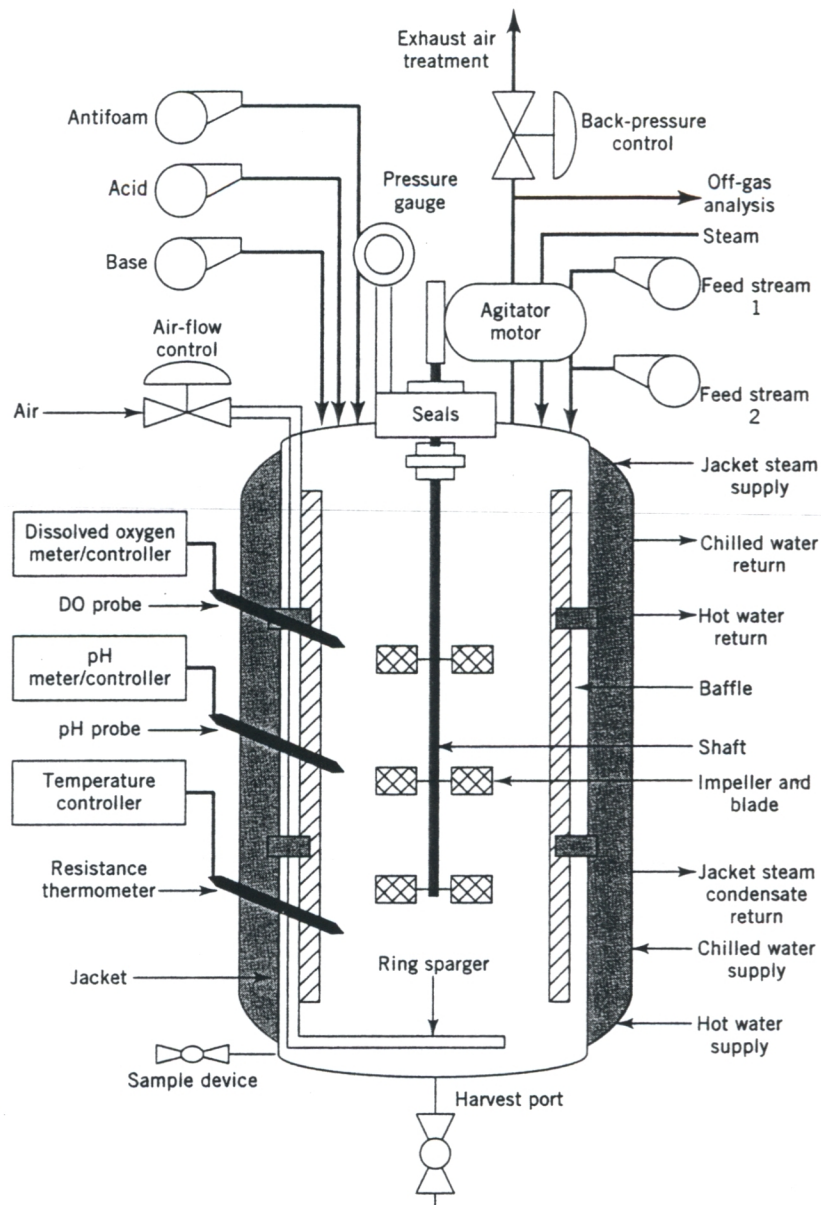
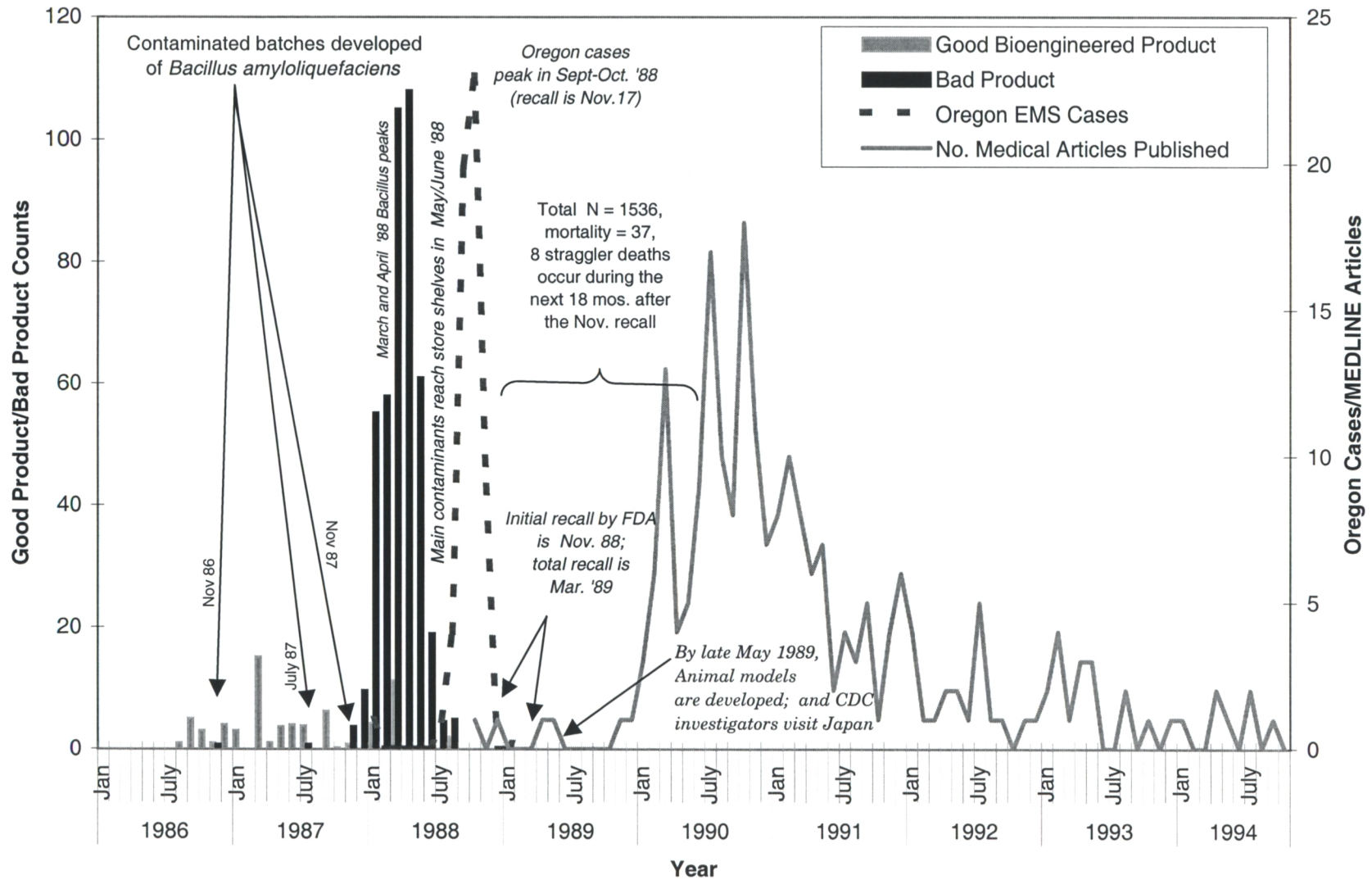


Fig. 1. Representation of a jacketed fermentor.

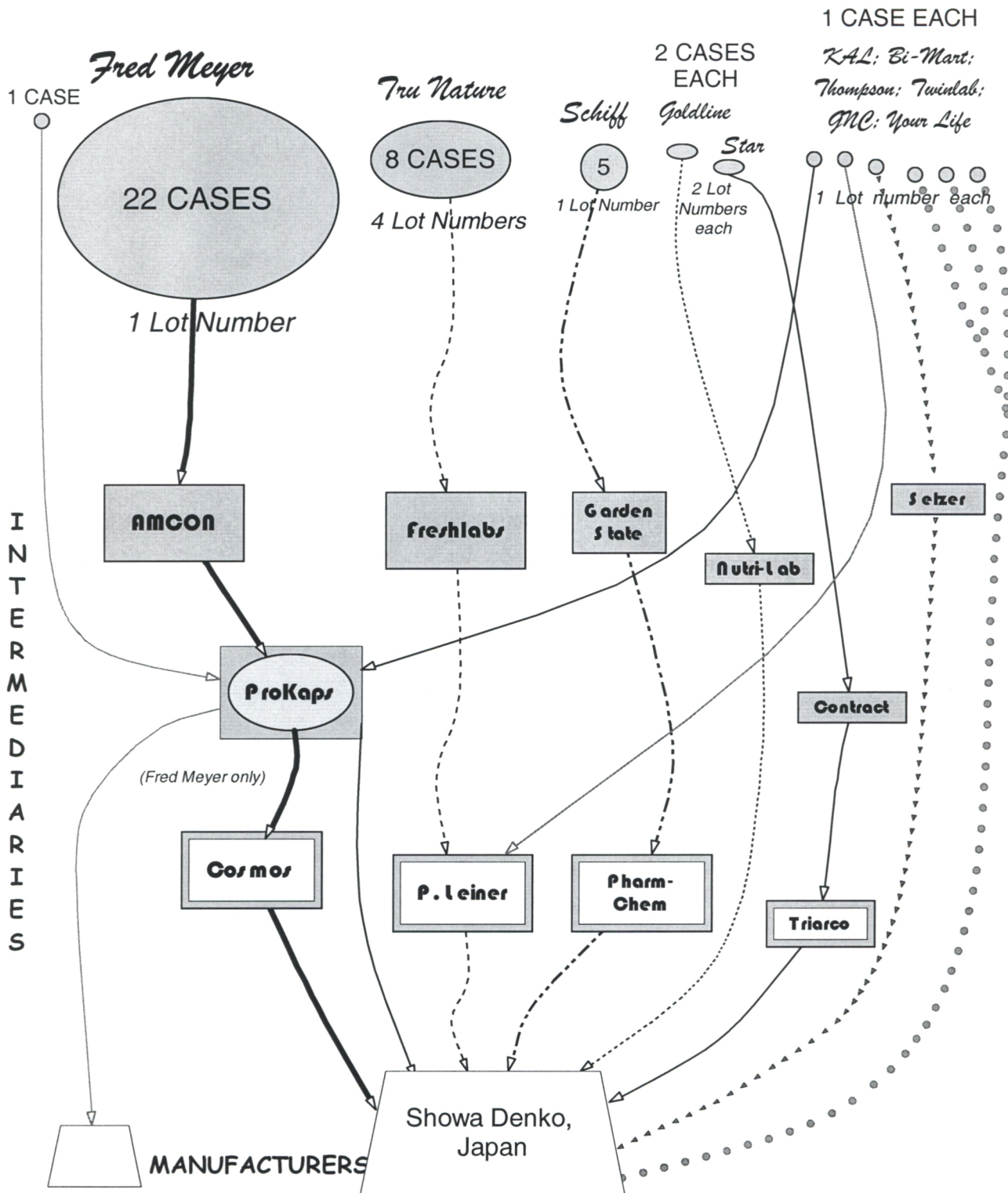
icillin G production. Generally, fermentation in the production vessel continues for 2–7 days depending on the nature of the product, the process, and the micro-organism employed. Many products such as fine chemicals and some enzymes are manufactured on small scales necessitating production vessels of only a few thousand or even a few hundred liters. For these smaller systems, the associated seed-train vessels are also smaller.

From an operational viewpoint, there are many differences between some of the traditional fermentations and those employing cloned or genetically engi-

Oregon Cases and Professional Medical Journal Articles on TRP relative to TRP Contamination Process



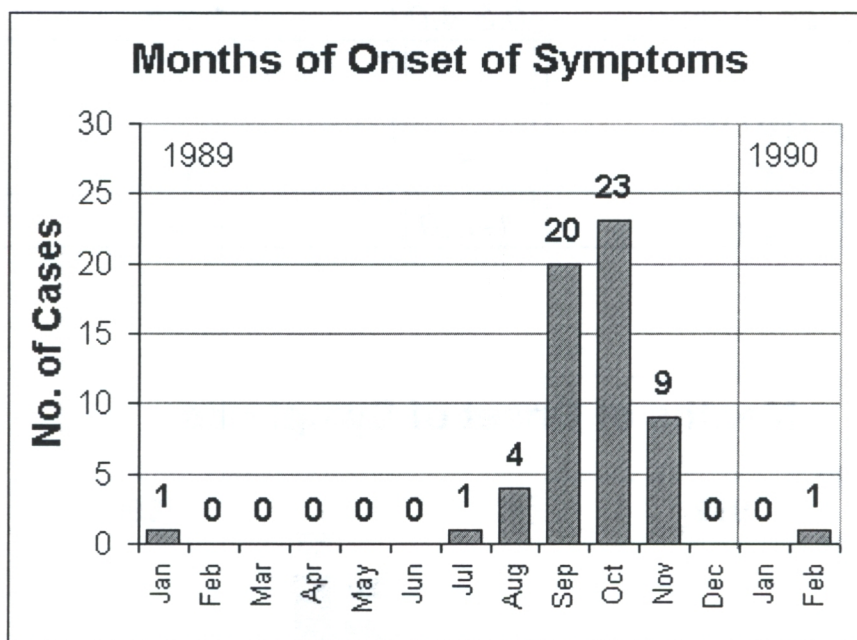
Tracing the Contaminated Tryptophan, 46 Cases, Oct 1989 to Feb1990



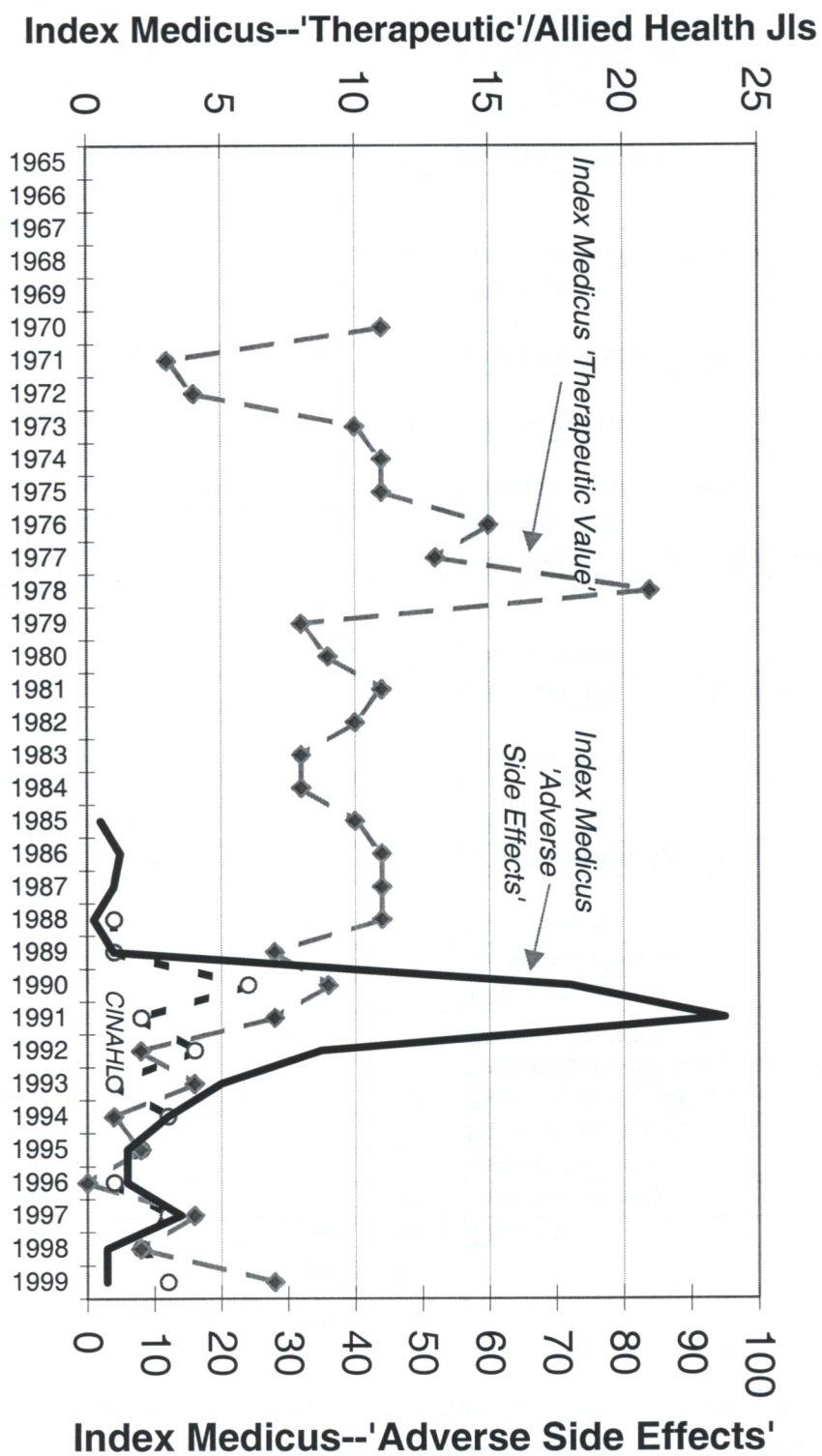
Prevalence of TRP Use by Age and Sex in Oregon, 1989

(Slutsker et al., JAMA 264; 215; July 11, 1990)

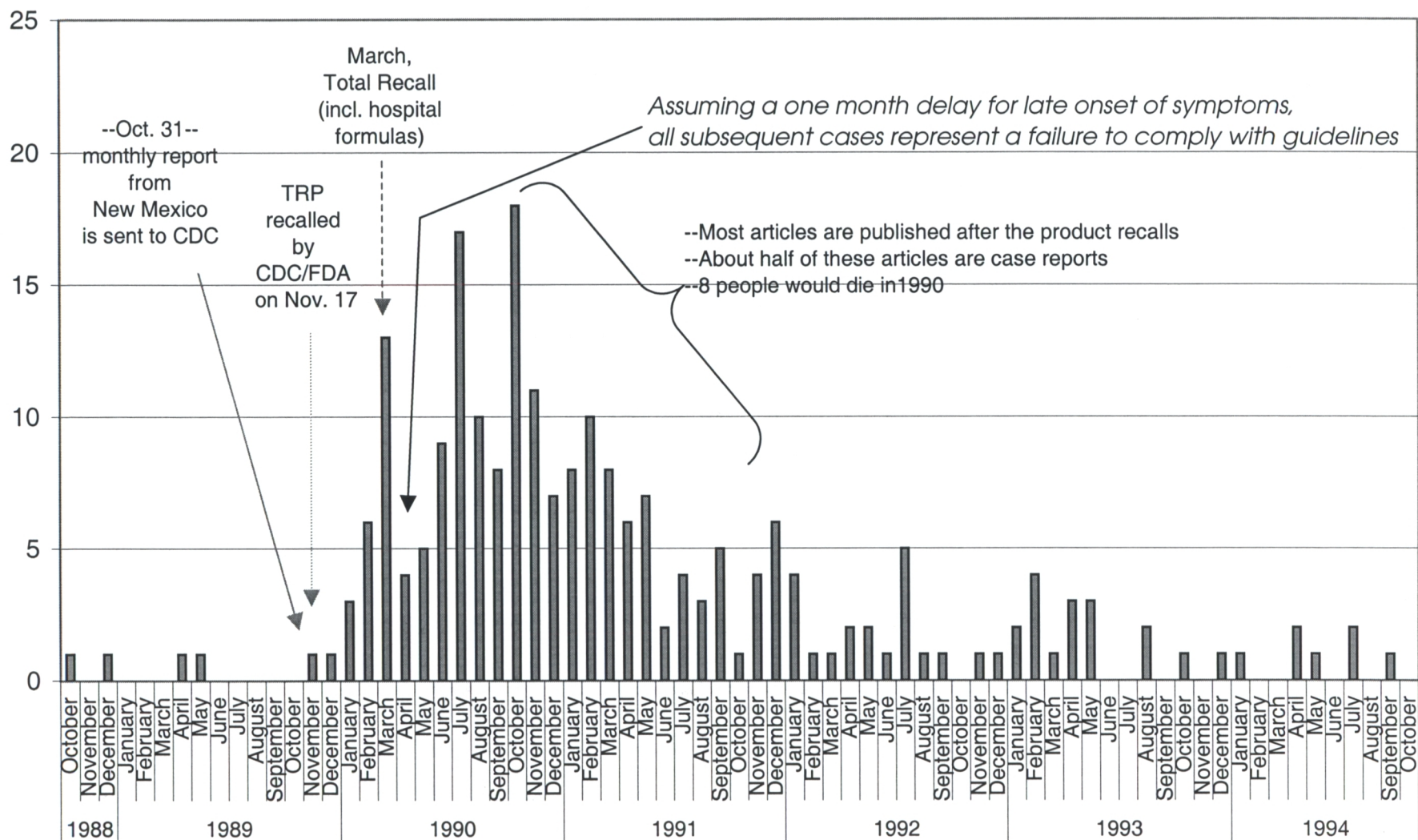
AGE	Males	%	Females	%	Total	%
0-20	0/12	0	0/17	0	0/29	0
21-39	1/135	0.7	4/158	2.5	2/293	1.7
40-59	2/96	2.1	5/121	4.1	7/217	3.2
>60	3/78	4	1/113	1	4/191	2
Total	6/321	1.9	10/409	2.4	16/730	2.2



Medical Journal Articles published on Tryptophan Side Effects and Therapeutic Value, 1970 to 1999



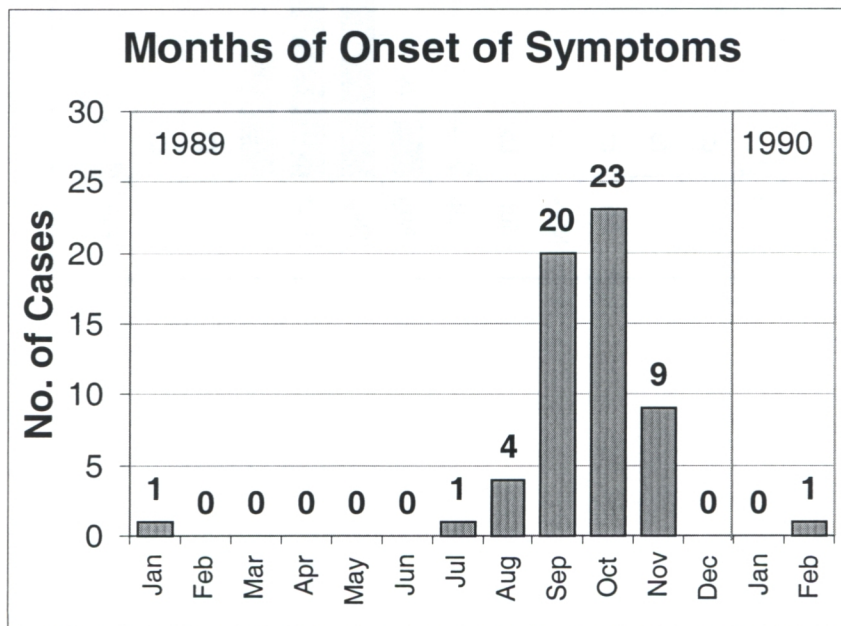
Number of Articles on the "Adverse Effects" of Tryptophan published in Medical Journals, November 1989 to October 1994



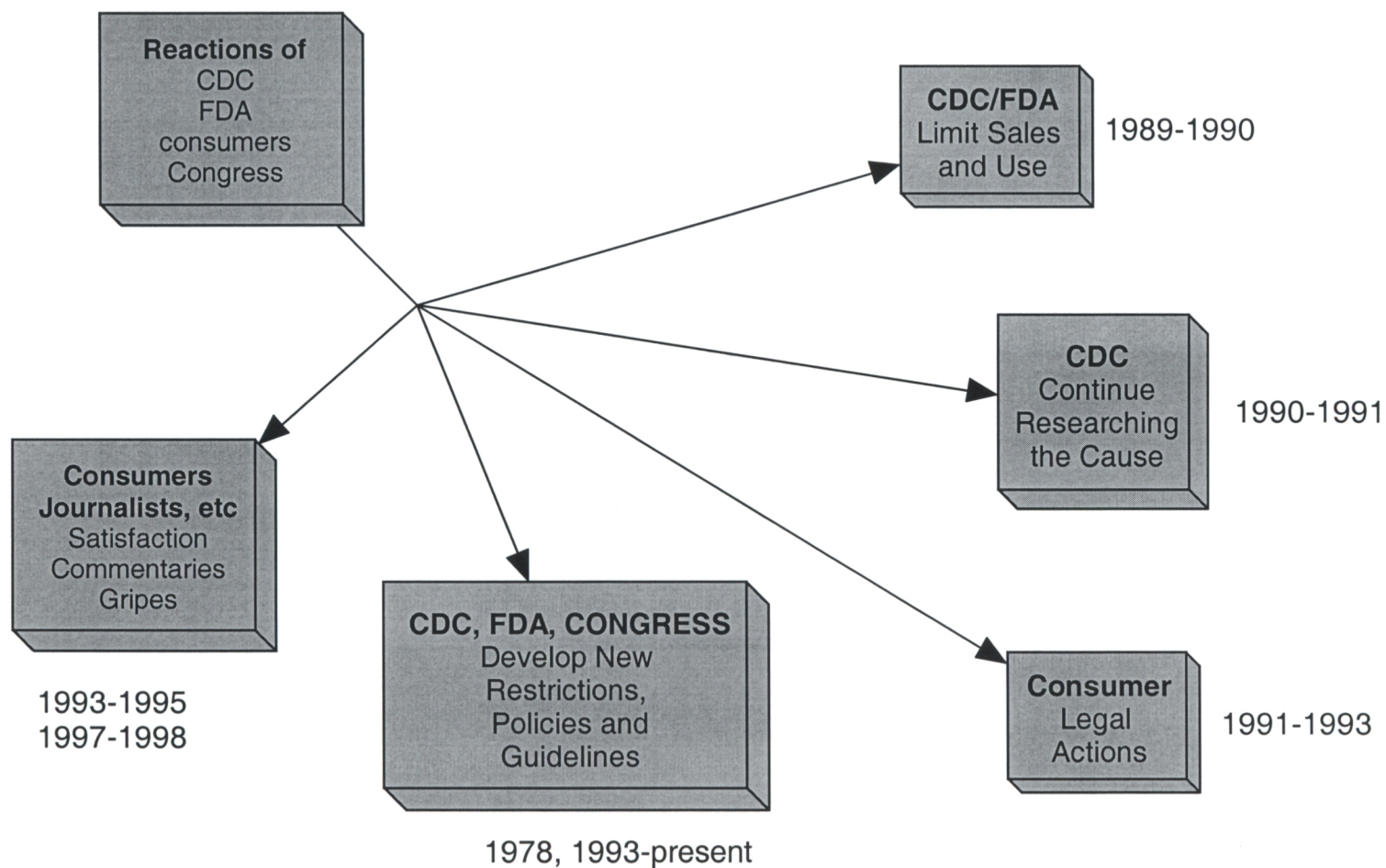
Oregon Tryptophan Cases

(Slutsker et al., *JAMA* 264; 215; July 11, 1990)

	Cases	Controls	
		<i>Telephone Survey</i>	<i>Volunteer Callers</i>
Subjects	58	30	63
Median Age	50	51	42
Range	29-78	25-81	24-84
% Female	91	80	81
TRP Dosage, g/day, median	1.3	0.4	0.5
Range (g/day)	0.3-4.0	0.1-3.5	0.1-4.0
Duration of TRP use, months, median	7	18	18
Range (mos)	1-120	1-108	1-132



Results of the October 1989 to February 1990 Tryptophan Episode



TRP Articles in Cumulative Index to Nursing and Allied Health Literature
(relative to Nov 1989, date of the CDC announcement and recall)

Journal	(Number of articles)		Topics
	Before	After	
Newsweek	1	0	insomnia remedy
Psychology Today	1	0	insomnia remedy
Physical Therapist	1	0	Relief of Burning Pain
Nurses' Drug Alert	5	2	Pain, Co-medication with anti-depressants, Carbohydrate-fatigue, neurotoxicity; recall, the manufacturer
RN	0	1	TRP and pasta
Physician Assistant	0	1	the legacy of its use
News for the Legal Nurse Consultant	0	2	Legal issues
Hospital Practitioner	0	1	Erythromyalgia Syndrome
California Berkeley Wellness Letter	0	1	Issues
Harvard Medical School Health Letter	0	1	"Natural Disaster"
Chiropractic Journal	0	1	OTC and "the truth" about TRP
Journal of the American Dietetic Association	0	2	Toxicity Issue
American Journal of Clinical Nutrition	0	3	TRP and the serotonin path; exercise and recovery; CNS
Journal of Laboratory and Clinical Medicine	0	1	Lung/respiration activity
Alternative Medicine Review	0	1	5-hydroxy-TRP
Journal of Musculoskeletal Pain	0	1	Therapeutic efficacy--IL-5 interference; recovery
Office Nurse	0	1	TRP in pasta
	0	2	purchasing TRP; TRP for memory
Alternative Health and the Conscious Individual			
Canadian Journal of Applied Physiology	0	1	Exercise and TRP
Alternative Medicine	0	1	5-hydroxy-TRP
Emergency Medicine	0	1	the legacy of its use
Archives of Physical Medicine and Rehabilitation	0	1	EMS recovery

A Review of TRP articles in *The Readers' Guide to Periodical Literature*

Before/After FDA withdrawal

Journal	Before	After	Issues
Prevention	7	0	Insomnia, Pain, Obesity, Cholesterol, Blood Pressure; General
Psychology Today	4	0	Insomnia, Pain, Aggression
Newsweek	1	0	Insomnia
Mademoiselle	1	0	Insomnia
Health	1	0	Infant Sleep
Saturday Evening Post	1	0	Depression
US and World News	0	1	Pain
People's Weekly	0	1	OTC Issue
Consumer Research Magazine	0	1	OTC Issue
Readers' Digest	0	1	OTC Issue
FDA Consumer	0	2	OTC Issue
Skeptical Inquirer	0	1	OTC Issue
In Health	0	1	OTC Issue
Science News	1	1	Therapeutic value; hepatic physiology; mother-fetal development (maternity)
Discover	0	1	OTC Issue; maternity
Total	16	10	

TRP-related Articles in Popular and Business Magazines

(Sources: 1986-1995: Business Source Elite; Master File Premier [EBSCO Host Search Engines])

Journal	BSE	MFP	Supports Use?	
			Before	After
People				
Woman's Day			Y?	Y?
Cosmopolitan				Y
Essence				
Forum				
Readers' Digest				Y
New York Times			Y?	Y
American Health			Y	
Health Line			Y	
Nutrition Forum			Y	Y
Nutrition Today			Y	Y
Better Nutrition for Today's Living			Y	Y
Environmental Nutrition			Y	
Health Weekly			Y	
Total Health			Y	
National Health			Y	
Nutrition Action and Health Letters			Y	
Cortlandt Forum			Y	
Vegetarian Times			Y?	
Organic Gardening			Y?	
Women's Health Weekly			Y?	
Horizons			Y?	
Mothering			Y?	
Parenting			Y?	
Men's Health			Y	Y
Joe Weider's Muscle and Fitness			Y	Y
Shape			Y	Y
Body Bulletin			Y	Y
Self			Y	Y

Journal	BSE	MFP	Supports Use?	
			Before	After
New Scientist				
Journal of Studies on Alcoholism			Y	Y
Journal of Nutrition			Y	Y?
Journal of Nutritional Medicine			Y	Y?
American Journal of Psychology			Y	Y?
International Review of Psychology			Y	Y?
Psychopharmacology Update			Y	Y?
Social Policy			Y	Y
Consumer Research			Y	N?
FDA Consumer				N
Newsweek				
Forbes				
Issue				
Restaurant Business			Y	Y
LA Business Journal				
Economist				
Wall Street Journal			Y?	
Success				
Time (Canada)				
Food Technology			Y	Y
Chemical Marketing Reporter			Y	Y
Chemical Week			Y	Y
University of Calif, Berkeley Letter			Y?	N?
Health Letter on the CDC			Y?	N
NCRHI				N
Harvard Health Letter			Y?	N?

Classification Type	Description of equation <i>(Partial=1/2)</i>
Psychiatric	Depression, affective disorders, mania, bipolarism, schizophrenia
Behavioral Psychology	Total inclusion for: bulimia, insomnia, alcoholism, attention deficit. Partial inclusion for: depression, affective disorders.
Neuromuscular	Parkinsonism, myoclonus, migraine, Tardive Dyskinesia, Rett syndrome
Pain	Includes disease-related, post-surgical, and post-trauma pains, headaches; partial arthritis and anti-inflammatory uses.
Chronic Disease	Epilepsy, rheumatoid arthritis, cancer
Aging	Total inclusion of Alzheimers. Partial inclusion of: Arthritis, insomnia, depression, insomnia, dermal problems, renal problems, hypertension.

CHRONOLOGY

- 1938 Food, Drug and Cosmetic Act: Food and Drug amendments are passed, requiring proof of safety and efficacy.
- 1941 FDA publishes Minimum Daily Requirements for vitamins and supplements.
- 1949 Certain amino acids are link to neurochemical paths, making them potentially marketable as prescriptional products once their efficacy is tested.
- 1958 Food Additives Amendment (proof of safety before marketing)
- 1962 New Food and Drug amendments are passed, requiring proof of safety and efficacy followed by premarket approval; effectiveness must be shown by producer/sponsor.
- 1970s Development of *Bacillus* species bacterial cell cultures for food additive production
- 1973 FDA limits potency (high potency supplement = "drug"); new list of Generally-Regarded as Safe Substances [GRAS] is produced (without amino acids included).
- 1976 Supplements with misleading claims are considered subject to seizure by FDA
Congress responds with the Proxmire Amendment, which restricts FDA's authority: 1) cause must be related to safety; 2) large dosage supplements may not be restricted or termed "drugs." FDA seizes amino acid products.
- 1977 FDA actions are reversed due to "accidental" inclusion of amino acids on GRAS list, due purportedly to "typographical error." Grant et al. (1977) demonstrated the possible formation of toxic metabolites from Tryptophan when placed in parenteral solutions (a sodium bisulfite-preservative induced reaction process).
- 1980s TRYPTOPHAN (TRP) becomes a popular nutritional supplement. Chief use: as a sleep promotor due to conversion into Serotonin within the central nervous system. Other uses: migraine headaches, anxiety, depression, PMS, stress, jet lag, and memory problems. Large dose usage: cancer, urinary bladder infection, Lupus, diabetes, scleroderma. Side Effects/Complications: bronchial asthma aggravation, liver damage (author's claim).
- TRP and other protein-derived amino acids are produced through a fermentation or denaturation process; much of this manufacturing process is done in Japan; bacterial genotype does not undergo any modification.
- 1988 Tryptophan products are manufactured from a bioengineered *Bacillus amyloliquifaciens*; early cultures produce various toxins and by-products not found to be at high levels.
- Mid-1988 *Bacillus* cultures are again modified in their growth medium, with changes made as well on carbon filtration methods.
- 1989 October 30th. Tablets of (TRP) taken for sleep problems and depression are blamed for Three DEATHS in New Mexico by the New Mexico Department of Health and Environment. Cause for death is determined to be Eosinophilia-Myalgia Syndrome (EMS).
- [CDC. MMWR 1989; 38: 765-767.]
- [CDC. MMWR 1989; 38: 785-6. New Mexico, Minnesota, Oregon and New York].

- 1989 November 15th. Thirty more cases of EMS were identified in New Mexico; half of these victims were hospitalized due to debilitating muscular pain, accompanied by fever, arthralgia, shortness of breath, rashes, edema, pneumonia and general weakness (Hunter 1990). A total of 360 cases of EMS were identified by CDC, including one more death; all of these cases could be linked to recent tryptophan use.
- November 17th. NATIONWIDE RECALL is announced by FDA, for all nutritional supplements containing tryptophan as a major constituent.
- 1990 January to early February. Fifty states, DC and Puerto Rico reported 1298 EMS cases to the CDC, including 15 deaths. Newborn infant case noted in which the expecting mother had taken TRP for four months prior to delivery. 35 more deaths and 1500 cases ensue during the months following the recall.
- March. NATIONWIDE RECALL or all TRP-containing dietary supplements, including infant formulas, protein supplements, and special dietary foods.
- March 16th. 1411 cases and 19 deaths noted by CDC. Case example reported to CDC: patient began use of TRP March 20th, and developed symptoms one month later.
- April.
- JAMA 1990; 264. Contaminated TRP is linked to a single manufacturer.
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- August 24. 1536 cases of EMS.
- October.
- CDC Report. High Pressure Liquid Chromatography revealed a peak (Peak 97) indicative of bad batches of TRP, usually associated with EMS. [JAMA, October 30, 264: 1656]
- Criteria for diagnosis: eosinophilia \geq 1000 eosinophils and severe, debilitating myalgia.
- Most cases which developed after the FDA recall on February 1, 1990 were due to latent onset. Only 8 new cases were recorded by CDC as due to continued use by patient in spite of recall. FDA commissioned the Federation of American Societies for Experimental Biology (FASEB) to review amino acid use and safety. (1992—FASEB determined that no conclusions could be drawn, and recommended that use be monitored by professionals.)
- October. Suspected chemical form of toxin is published on October 3rd.
- November. Exact nature of toxin deduced and published Nov. 28th.

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