

54929

AN APPRAISAL OF THE
FDA RISK ANALYSIS FOR
PCB-CONTAMINATED FISH AND ITS
RELEVANCE TO REGULATORY ACTIONS
ACTIONS AT NEW BEDFORD HARBOR

Prepared for

Ropes & Gray
225 Franklin Street
Boston, Massachusetts 02110

by

L. Daniel Maxim, Ph.D.
Everest Consulting Associates, Inc.
15 North Main Street
Cranbury, New Jersey 08512

8 January 1987

Attachment-XIX-12

Background

Polychlorinated Biphenyl (PCB) is the name given to a series of chemical compounds produced industrially by chlorination of biphenyl with anhydrous chlorine and iron filings or ferric chloride as a catalyst.¹ Industrially produced PCB preparations contain PCBs with varying degrees of chlorine substitution on the biphenyl ring with generic formula, $C_{12}H_{10-r}Cl_r$, where r is the total number of chlorine atoms per molecule. PCBs were manufactured in the United States by Monsanto under the tradename Aroclor, and by manufacturers in other countries under other tradenames, including Kanechlor in Japan, and Clophen in West Germany. Table I shows the approximate percent composition according to degree of chlorine substitution of these commercial mixtures. PCB releases in the Acushnet River estuary consisted of Aroclors 1254 and 1242.²

The homologous series of PCBs depicted in Table I can be further partitioned into various congeners, based upon the position in the biphenyl molecule where substitution occurs. In all, some 209 distinct congeners arise from the combinatorial substitution possibilities, although not all of these congeners can be found in each or all of the commercial mixtures. (This disaggregation is appropriate because, as discussed below, there are important differences in the biological activity among the various congeners.) Figure I shows the substitution nomenclature and combinatorics for the PCB molecule.

Concern over possible effects on human health from eating foods contaminated with PCBs dates back to the early 1970s when several instances of accidental food contamination and adverse human health effects were discovered.³ Fish and shellfish

¹Hutzinger, O., S. Safe, and V. Zitko, The Chemistry of PCBs, CRC Press, Boca Raton, Florida, 1980, p. 8.

²Brown, J. F., Jr., and R. E. Wagner, Polychlorinated Biphenyl (PCB) Movement and Transformation in Acushnet Estuary Sediments, General Electric Research and Development Center, 26 September 1986, p. 1.

³It is now generally believed that polychlorinated dibenzofurans (PCDFs), a contaminant present in the Yusho and Yu-Cheng incidents occasioned the adverse health effects rather than PCBs (U.S. EPA, Health Assessment Document for Polychlorinated Dibenzofurans, EPA/600/8-86/018A, June 1986, Review Draft, p. 7-27.).

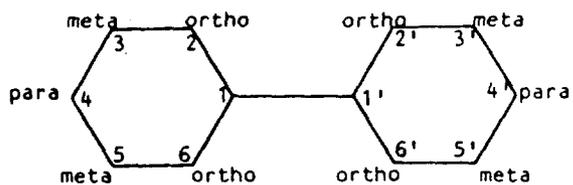
TABLE I.
APPROXIMATE PERCENT COMPOSITION OF SOME COMMERCIAL PCB PRODUCTS

	Aroclor Type or Grade							Kanechlors			Clophens	
	1016	1221	1232	1242	1248	1254	1260	KC-300	KC-400	KC-500	A 30	A 60
Polychlorobiphenyl												
C ₁₂ H ₁₀	<0.1	11	6	<0.1	-	<0.1	-	-	-	-		
C ₁₂ H ₉ Cl	1	51	26	1	-	<0.1	-	-	-	-		
C ₁₂ H ₈ Cl ₂	20	32	29	16	2	0.5	-	17	3	-		
C ₁₂ H ₇ Cl ₃	57	4	24	49	18	1	-	60	33	5		
C ₁₂ H ₆ Cl ₄	21	2	15	25	40	21	-	23	44	27	Similar	Similar
C ₁₂ H ₅ Cl ₅	1	0.5	0.5	8	36	48	12	0.6	16	55	to	to
C ₁₂ H ₄ Cl ₆	<0.1	-	-	1	4	23	38	-	5	13	1232	1260
C ₁₂ H ₃ Cl ₇	-	-	-	<0.1	-	6	41	-	-	-		
C ₁₂ H ₂ Cl ₈	-	-	-	-	-	-	8	-	-	-		
C ₁₂ H ₁ Cl ₉	-	-	-	-	-	-	1	-	-	-		
C ₁₂ Cl ₁₀	-	-	-	-	-	-	-	-	-	-		
Average % Chlorine	42%	21%	32%	42%	48%	54%	60%	~ 42%	48%	54%	30%	60%

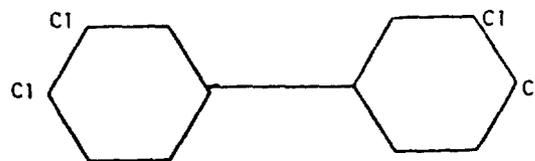
Sources: Polychlorinated Biphenyls, The National Research Council, National Academy of Sciences, Washington, D.C. 1979.
Hutzinger, O., S. Safe, and V. Zitko, The Chemistry of PCBs, CRC Press, Boca Raton, Florida, 1980, p. 8.
Michael, Paul, Monsanto, personal communication.

**FIGURE 1.
STRUCTURE, SUBSTITUTION NOMENCLATURE,
AND NUMBERING SYSTEM FOR PCBs**

Substitution Nomenclature
and Numbering System for PCBs



A Specific Example



3, 3', 4, 4' Tetrachlorobiphenyl

Chlorine Atoms On First Ring

	0	1	2	3	4	5
0	1	3	6	6	3	1
1		6	18	18	9	3
2			21	36	18	6
3				21	18	6
4					6	3
5						1

Chlorine Atoms
On Second Ring

Possible distribution of chlorine atoms in the two rings of biphenyl.

PCB levels have been of particular concern because ingestion of contaminated foods is thought to be a major pathway to human exposure and PCB levels in fish are often greater than corresponding levels in other foods. The Food and Drug Administration (FDA), acting in accord with its mandate under Section 406 of the Federal Food, Drug, and Cosmetic Act (FFDCA), first imposed a temporary tolerance level of 5 parts per million (ppm) PCBs in the edible portion of fish. Later this tolerance level was reduced to 2 ppm.⁴ Fish above this limit were not permitted to enter interstate commerce.

The FDA regulatory action, coupled with measured data showing that some PCB levels in fish and shellfish in the Acushnet estuary and contiguous portions of Buzzards Bay, exceeded the tolerance level led to a series of advisory and regulatory actions by the Massachusetts Department of Public Health (DPH) culminating in the closure of three designated geographic areas to the taking of various fish and shellfish on 25 September 1979.⁵

As this action, inter alia, forms the basis for the natural resource damage claims in this suit, it is important to review the basis for FDA's establishing a 2 ppm tolerance level for PCBs in fish and shellfish.

This paper summarizes and critiques the risk analysis which formed the foundation for the establishment of the 2 ppm tolerance level. Site-specific information is discussed, where appropriate, to contrast the assumptions made by FDA with the relevant facts in this case.

⁴See Federal Register, Volume 38, 6 June 1973, p. 18096, also Volume 42, Number 63, 1 April 1977, pp. 17487 et seq., Volume 44, Number 127, 29 June 1979, pp. 38337 et seq., and Volume 49, Number 100, 22 May 1984, pp. 21514 et seq.

⁵Kolek, A. and R. Ceurvels, "Polychlorinated Biphenyls (PCB) Analysis of Marine Organisms in the New Bedford Area 1976-1980," Commonwealth of Massachusetts, Division of Marine Fisheries, January 1981, p. 1.

Overview of the FDA Risk Estimation Process Used to Justify the 2 ppm Standard

The evidence used to justify the 2 ppm tolerance or action level was based, in part, upon a quantitative risk analysis^{6, 7} conducted by FDA that extrapolated the purportedly carcinogenic effects of high PCB doses administered to laboratory animals to the low dose levels typically associated with human consumption of contaminated fish. Given the assumed correspondence between estimated health risk and content of PCBs in the diet of Americans, FDA was able to set a tolerance level for PCBs in fish that entailed (at least implicitly) an "acceptable" risk.

The steps required to make this extrapolation are outlined in Figure 2. Letters shown above the boxes are used to refer to these computations later in this paper. Broadly, FDA first had to estimate the average (and 90th percentile) daily PCB intake for humans who eat fish species contaminated with PCBs. This was then adjusted to simulate the effect of imposing a specific tolerance level, such as 5 ppm. Next, human risks were estimated from high dose animal cancer studies using a so-called "one-hit" dose-reponse model for extrapolation purposes. A 99% upper confidence limit to this risk was then calculated to provide a margin of safety. These computations were replicated for other assumed tolerance levels (i.e., 2 and 1 ppm) to determine approximately how the health risks (as measured by the number of probability of additional cancers) varied with the assumed tolerance level. In parallel, other studies addressed the economic consequences (measured by the loss of food supply as required by the FFDCA) of the imposition of various tolerance levels. Finally, a judgmental balance was established and

⁶Food and Drug Administration (1979), "An Assessment of Risk Associated with Human Consumption of Some Species of Fish Contaminated with Polychlorinated Biphenyls PCBs", Food and Drug Administration, Exhibit 45, prepared by PCB Risk Assessment Work Force, Joseph Rodricks, Chairman.

⁷Cordle, R. Locke, and J. Springer (1982), "Risk Assessment in a Federal Regulatory Agency: An Assessment of Risk Associated With the Human Consumption of Some Species of Fish Contaminated with PCBs," Environmental Health Perspectives, Volume 45, pp. 177-182.

FIGURE 2.
LOW DOSE EXTRAPOLATION METHODOLOGY

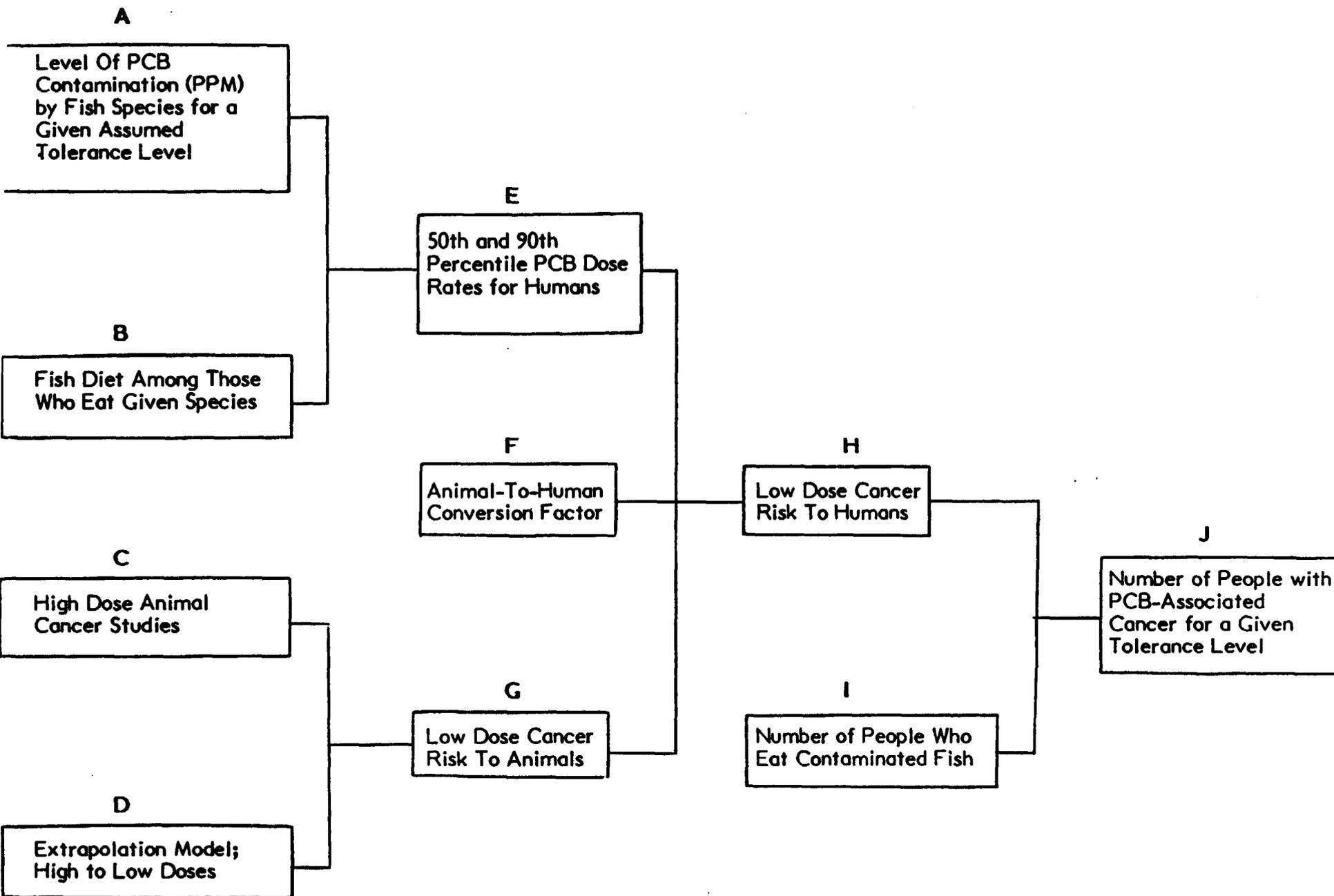


TABLE 3.
UNCERTAINTY, CONSERVATISM, AND RESULTING CONSEQUENCES IN RISK ANALYSIS
 (continued)

QUOTE	REFERENCE
<p>"Recent research has also shown a need to reevaluate the role of 'conservatism' in assessing and managing risk. Making a 'conservative decision' (i.e., one that is likely to be more protective of health and the environment than an alternative decision) is widely accepted as a prudent practice in risk management. <u>In keeping with the recommended separation of risk assessment and risk management activities, however, conservative assumptions, conservative models, conservative estimates, etc., should not be key elements in the science-based risk estimation steps. A catenation of conservative assumptions, models, and estimates throughout a risk assessment can lead to a worst-case' (or even worst-of-the-worst-cases) prediction that may be of little value (or possibly misleading) to the decision maker.</u> Most decisions actually involve 'either-or' choices between technological alternatives with different risk levels rather than a 'yes-no' choice on a single risk. When dissimilar alternatives require different analysis procedures, conservatism ambiguously or inconsistently applied could lead to biased results and poor decisions — even to the choice of a technology that is less protective of human health and the environment and possibly more costly to society than an available alternative. Best estimates of the risks, costs, and benefits for the alternatives, coupled with consideration of their uncertainties (including worst-credible case considerations), should produce the optimal basis for decision making. The Council on Environmental Quality has recently noted that 'rules of reason' should replace worst case analysis as the basis of regulatory decision making (CEQ, 1985, 1986)."(Emphasis added)</p>	<p>Midwest Research Institute, <u>Risk Assessment Methodology For Hazardous Waste Management, Draft Final Report</u>, prepared for EPA under Contract No. EQ4C15, 31 July 1986.</p>

A Critique of the FDA Risk Analysis

- Beginings

To begin, it is important to note that there are no data suitable for direct estimation of PCB cancer potency in humans. Indeed, there is insufficient evidence on which to base any conclusion that PCBs are carcinogenic in humans⁹ -- a point made elsewhere in testimony in this case and acknowledged by FDA. Rather, indirect (and mixed) evidence is furnished from experiments with rats and mice.¹⁰ These experiments were conducted at elevated doses (25 ppm to 300 ppm in feed) so as to increase response rates and lower requisite animal sample sizes, as is common in studies of this type. The NCI study on Aroclor 1254 used, inter alia, as a basis for FDA's risk estimates shown in Table 2 actually stated,¹¹

"It is concluded that under the conditions of this bioassay, Aroclor 1254 was not carcinogenic in Fischer 344 rats,"

a finding that can hardly be termed supportive of FDA's conclusions.

This observation aside, such a protocol necessitates conversion of results between species (e.g., from mice to humans) and extrapolation of results from the high experimental doses to lower doses more commonly found in environmental exposure. The

⁹Drill, Friess, Hays, Loomis, and Schafer, Inc., Potential Health Effects in the Human From Exposure to Polychlorinated Biphenyls and Related Impurities, Arlington, Virginia, February 1982. See also related report from the same firm, dated 12 February 1982. PCBs are classified 2B in the IARC weight-of-evidence designation (probably carcinogenic in humans; evidence inadequate in humans and sufficient in animals). This is similar to the EPA designation "B2." See also U.S. Environmental Protection Agency, Development of Advisory Levels for Polychlorinated Biphenyls (PCBs) Cleanup, prepared by Exposure Assessment Group, Office of Health and Environmental Assessment, Washington, D.C., OHEA-E-187, May 1986, Final p. D-16.

¹⁰The State of California and others place PCBs in the category of "chemicals for which there is sufficient evidence of carcinogenity in experimental animals." See State of California, Health and Welfare Agency, Department of Health Services, Guidelines for Chemical Carcinogen Risk Assessments and Their Scientific Rationale, November 1985, p. B-31.

¹¹National Cancer Institute Bioassay of Aroclor 1254 For Possible Carcinogenicity, NCI Carcinogenesis Technical Report, Series No. 38, CAS No. 27323-18-8, NCI-CG-TR-38, 1978.

mechanics of this conversion and extrapolation are subject to much uncertainty and are ultimately contentious. A partial listing of relevant factors includes,¹²

- (i) choice of extrapolation model,
- (ii) background adjustments,
- (iii) statistical fitting procedures used,
- (iv) type of estimate (expected value or upper confidence level)
- (v) dose and exposure assumptions (e.g., effects of cooking, congeners of interest, levels over time)
- (vi) species to human extrapolation basis,
- (vii) response variable measured, and
- (viii) animal experiment used for estimation of the dose-response curve and the specific health effect used.

Additionally, with respect to complex mixtures such as PCBs, it is important to identify precisely the allegedly hazardous compounds (congeners in this case) at issue. This later point is singularly important in this case because there is evidence that the mixture of congeners being released from the Acushnet sediments is quite different from those commercial mixtures used in the animal experiments.

- Differential Toxicity

For example, the study generally regarded as providing the most convincing evidence of the carcinogenicity of PCBs in rats¹³ is that conducted by Kimbrough et al.¹⁴ This

¹²Maxim, L. Daniel, and Leigh Harrington, Everest Consulting Associates, Inc., "A Review of the Food and Drug Administration Risk Analysis for Polychlorinated Biphenyls in Fish," Regulatory Toxicology and Pharmacology, Volume 4, Number 2, June 1984.

¹³Crump, K. S., and M. D. Masterman, Assessment of Carcinogenic Risks From PCBs in Food, prepared for United States Congress, Office of Technology Assessment, April 1979, p. 24.

¹⁴Kimbrough, R. D., et al., "Induction of Liver Tumors in Sherman Strain Female Rats by Polychlorinated Biphenyls Aroclor 1260," Journal of the National Cancer Institute, Volume 55, 1975, pp. 1453 et seq.

Kimbrough study used Aroclor 1260, a mixture containing approximately 60% chlorine (q.v. Table I). Further, there is evidence from numerous studies that the biological activity of PCBs is a function of the degree of chlorination:

- (i) Feeding experiments over 224 days with Kanechlor 300, 400, and 500 in mice were conducted by ITO *et al.*¹⁵ Hepatocellular carcinomas were induced only by the highest chlorinated compound, Kanechlor 500 (q.v. Table I).
- (ii) A study by Schaeffer *et al.*¹⁶ indicated that at the end of an 800-day feeding experiment, the incidence of hepatocellular carcinoma in mice fed clophen A 60 (q.v. Table I) reached 61%, whereas only 3% of those fed clophen A 30 and 2% of the controls were similarly affected.
- (iii) Schaeffer, *et al.*,¹⁷ also note,

"Both the DHEW Subcommittee on Health Effects of PCBs and PBBs (1978) and Ecobichon (1975) have reported that the toxic potency of PCBs (hepatic enzyme induction, hepatocarcinogenic effect) increases with increasing chlorination and chlorine substitution in the para, ortho, meta positions, respectively."

These and other results support the notion of increasing biological hazard with increasing average degree of chlorination of PCB mixtures. Thus, Kimbrough's results with Aroclor 1260 thus have to be viewed as a "worst case;" production of 1260 only accounted for a minority of total domestic PCB production,¹⁸ and was not used at all in the Aerovox process. (Moreover, results discussed below indicate that the environmentally accessible PCBs in the Acushnet estuary are those with the least biological activity.) Based upon production statistics from 1957 until the early 1970s more Aroclor 1242 (42% chlorine) was produced than any other Aroclor commercial mixture.

¹⁵Ito, N., *et al.*, "Histopathologic Studies on Liver Tumorigenesis Induced in Mice by Technical Polychlorinated Biphenyls and its Promoting Effect on Liver Tumors Induced by Benzene Hexachloride," Journal National Cancer Institute, Volume 51, 1973, pp. 1637 *et seq.*

¹⁶Schaeffer, E., *et al.*, "Pathology of Chronic Polychlorinated Biphenyls (PCB) Feeding in Rats," Toxicology and Applied Pharmacology, Volume 75, 1984, pp. 278-288.

¹⁷Schaeffer, E., *et al.*, "Pathology of Chronic Polychlorinated Biphenyls (PCB) Feeding in Rats," Toxicology and Applied Pharmacology, Volume 75, 1984, pp. 286.

¹⁸Hutzinger, O., S. Safe, and V. Zitko, The Chemistry of PCBs, CRC Press, Boca Raton, Florida, 1980, p. 9.

The FDA was well aware of some of the conceptual problems posed by congener-specific toxicity or carcinogenic potential, as indicated in the 1979 Federal Register comments,¹⁹

"The proposal itself noted certain factors that complicate the evaluation of PCB toxicity (e.g., varying degrees of toxicity among the several forms of PCB's, the presence of toxic impurities such as chlorinated dibenzofurans in commercial preparations of PCB's, the differences in chemical composition between commercial PCB's and PCB residues in fish, and varying susceptibilities of different animal species to the toxic effects of PCB's): these complicating factors were also pointed out in some of the comments received on the proposal."

Lacking more definitive data on which to base a more sophisticated analysis, FDA chose to resolve such ambiguity in a conservative fashion.

An Aside: Structure Activity Relationships

Since the original risk analysis was prepared, substantial research has been conducted to elucidate what are termed structure-activity relationships (SARs) among the 209 PCB congeners.

The work of Safe and his colleagues is particularly noteworthy in this regard.²⁰⁻³³

¹⁹Federal Register, Volume 44, Number 127, 29 June 1979, pp. 38332.

²⁰Bandiera, S., K. Farrell, G. Mason, M. Kelley, M. Romkes, R. Bannister, and S. Safe, "Comparative Toxicities of the Polychlorinated Dibenzofuran (PCDF) and Biphenyl (PCB) Mixtures Which Persist in Yusho Victims," Chemosphere, Volume 13, Number 4, 1984, pp. 507-512.

²¹Gyorkos, J., M. A. Denomme, B. Leece, K. Homonko, V. E. Valli, and S. Safe, "Reconstituted Halogenated Hydrocarbon Pesticide and Pollutant Mixtures Found in Human Tissues: Effects on the Immature Male Wistar Rat After Short-Term Exposure," Canadian Journal of Physiology and Pharmacology, Volume 63, Number 1, 1985, pp. 36-43.

²²Haake, J. M., J. C. Merrill, and S. Safe, "The In Vitro Metabolism of Benzo(a)pyrene by Polychlorinated and Polybrominated Biphenyl Induced Rat Hepatic Microsomal Monooxygenases," Canadian Journal of Physiology and Pharmacology, Volume 63, Number 9, 1985, pp. 1096-1100.

Based upon acute studies and other indicates of biological activity an interesting pattern of SARs is becoming apparent; the most toxic PCB congeners have chlorosubstitution at both para positions, chlorosubstitution in at least one meta position of both phenyl rings and no ortho substituents -- a point illustrated in Figure 3 with some of the more toxic congeners (q.v. Figure 1 for nomenclature).

²³Halvorson, Michael R., Timothy D. Phillips, Steven H. Safe, and L. W. Robertson, "Metabolism of Aflatoxin B₁ by Rat Hepatic Microsomes Induced by Polyhalogenated Biphenyl Congeners," Applied and Environmental Microbiology, Volume 49, Number 4, April 1985, pp. 882-886.

²⁴Hayes, M. A., E. Roberts, M. W. Roomi, S. H. Safe, E. Farber, and R. G. Cameron, "Comparative Influences of Different PB-Type and 3-MC-Type Polychlorinated Biphenyl-Induced Phenotypes on Cytocidal Hepatotoxicity of Bromobenzene and Acetaminophen," Toxicology and Applied Pharmacology, Volume 76, 1984, pp. 118-127.

²⁵Hayes, M. Anthony, Stephen H. Safe, Dianna Armstrong, and Ross G. Cameron, "Influence of Cell Proliferation on Initiating Activity of Pure Polychlorinated Biphenyls and Complex Mixtures in Resistant Hepatocyte In Vivo Assays for Carcinogenicity," JNCL., Volume 74, Number 5, May 1985, pp. 1037-1041.

²⁶Leece, Bryan, Mary Anne Denomme, Rheel Towner, and S. M. Angela Li, "Polychlorinated Biphenyls: Correlation Between In Vivo and In Vitro Quantitative Structure-Activity Relationships (QSARs)," Journal of Toxicology and Environmental Health, Volume 16, 1985, pp. 379-388.

²⁷Parkinson, A., S. Safe, et al., "Immunochemical Quantitation of Cytochrome P-450 Isozymes and Epoxide Hydrolase in Liver Microsomes from Polychlorinated or Polybrominated Biphenyl-Treated Rats, A Study of Structure-Activity Relationships," The Journal of Biological Chemistry, Volume 258, Number 9, 10 May 1983, pp. 5967 et seq.

²⁸Robertson, Larry W., Andrew Parkinson, Stelvio Bandiera, Iain Lambert, Jill Merrill, and Stephen H. Safe, "PCBs and PBBs: Biologic and Toxic Effects on C57BL/6J and DBA/2J Inbred Mice," Toxicology, Volume 31, 1984, pp. 181-206.

²⁹Safe, Stephen, et al., "Effects of Structure on Binding to the 2, 3, 7, 8-TCDD Receptor Protein and AHH Induction-Halogenated Biphenyls," Environmental Health Perspectives, Volume 61, 1985, pp. 21-33.

³⁰Safe, Stephen, et al., "PCBs: Structure-Function Relationships and Mechanism of Action," Environmental Health Perspectives, Volume 60, 1985, pp. 47-56.

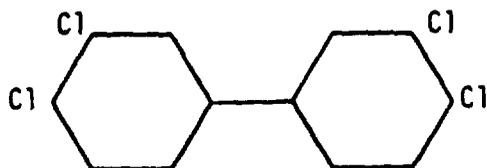
³¹Safe, Stephen, "Polychlorinated Biphenyls." In: H. F. Stich, ed. Carcinogens and Mutagens in the Environment, Volume V, Boca Raton, Florida: CRC Press, 1985.

³²Safe, Stephen, "Polychlorinated Biphenyls (PCBs) and Polybrominated Biphenyls (PBBs): Biochemistry, Toxicology, and Mechanism of Action," CRC Critical Reviews in Toxicology, Volume 13, Issue 4, pp. 319-396.

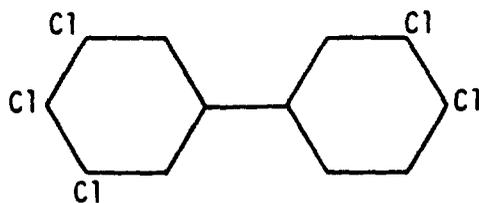
³³Safe, Stephen, Lorna Safe, and Michael Mullin, "Polychlorinated Biphenyls: Congener-Specific Analysis of a Commercial Mixture and a Human Milk Extract," Journal of Agricultural and Food Chemistry, Volume 33, 1985, pp. 24-29.

FIGURE 3.
EXAMPLES OF THE MOST TOXIC PCB CONGENERS

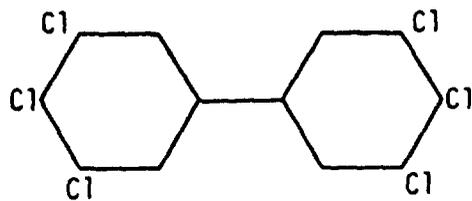
FORMULA



3,3',4,4' - Tetrachlorobiphenyl
or 34-34 CB



3,3',4,4',5 - Pentachlorobiphenyl
or 345-34 CB



3,3',4,4',5,5' - Hexachlorobiphenyl
or 345-345

COMMON FACTORS

- 1) Chlorosubstituents at both para positions,
- 2) Chlorosubstituents in at least one meta position of both phenyl rings, and
- 3) no ortho substituents.

Source: Safe, S., "Polychlorinated Biphenyls (PCBs) and Polybrominated Biphenyls (PCBs): Geochemistry, Toxicology, and Mechanism of Action," CRC Critical Reviews in Toxicology, Vol. 13, Issue 4, pp. 319, et seq.

Using various indicators of biological activity or potency, such as the capacity to cause thymic involution in rats or to induce aromatic hydrocarbon hydroxylase (AHH) the PCB congeners of greatest concern have been identified. These congeners are depicted in Figure 4.

Shifts in Congener Distribution

Interestingly, studies by Brown and Wagner³⁴ indicate that anaerobic bacterial dechlorination is taking place in the Acushnet estuary -- various PCB congeners are being attacked with reaction half lives of between 7 and 50 years. Most important, those congeners with greatest biological activity are among the most rapidly dechlorinated. Ultimately such shifts in congener distribution in the Acushnet sediments should be detectable in fish and shellfish, implying a concomitant decrease in health risk from human ingestion of fish and shellfish.

Return to the Main Theme: The FDA Risk Analysis

Basing the risk analysis, in part, upon the experiment that employed a commercial mixture (Aroclor 1260) expected to be relatively more potent is just one of the respects in which the FDA analysis can be termed conservative.

Maxim and Harrington³⁵ have noted several stages in the analysis at which conservative choices were made. Several of the more important are highlighted below.

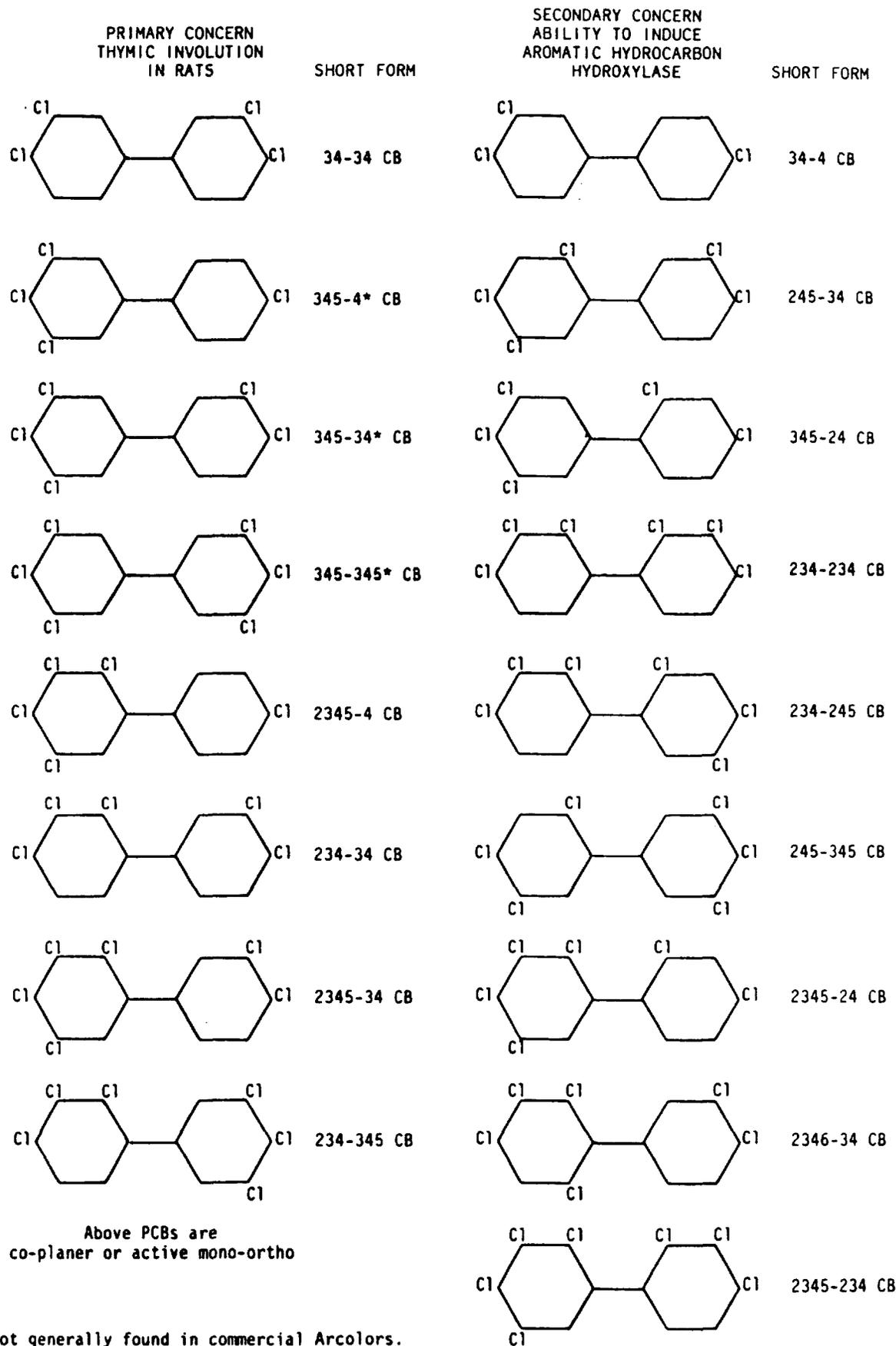
- Conservative Choice of Dose Response Model

The FDA chose a so-called "one-hit" model in which the probability of adverse response is given by,

³⁴Brown, J. F., Jr., and R. E. Wagner, Polychlorinated Biphenyl (PCB) Movement and Transformation in Acushnet Estuary Sediments, General Electric Research and Development Center, 26 September 1986.

³⁵Maxim, L. Daniel, and Leigh Harrington, Everest Consulting Associates, Inc., "A Review of the Food and Drug Administration Risk Analysis for Polychlorinated Biphenyls in Fish," Regulatory Toxicology and Pharmacology, Volume 4, Number 2, June 1987.

FIGURE 4.
PHARMACOLOGICALLY ACTIVE PCB CONGENERS
ATTACKED BY SYSTEM H AND H^I



*Not generally found in commercial Arcolors.

Source: Brown, J. F., Jr., and R. E. Wagner, "Polychlorinated Biphenyl (PCB) Movement and Transformation in Acushnet Estuary Sediments," General Electric Research and Development Center, 26 September 1986.

$$P(d) = 1 - \exp(-a d), \quad (1)$$

Where d = dose (in convenient units),

$P(d)$ = lifetime incremental cancer probability, and

a = constant to be determined from the data.

It assumes that a single biologically effective dose reacting with one receptor site within a cell is sufficient to initiate a cancer cell, and models the initiation as a poisson process.

It is important to recognize that numerous alternatives to the one-hit model have been proposed, including the Mantel-Bryan, Probit, Logistic, Extreme Value, Multistage, and Gamma multihit models. Results of Maxim and Harrington³⁶ indicate that the estimated risks are lower with each of these alternative models -- in some cases by several orders of magnitude.

It is generally acknowledged that use of the one-hit model is a conservative approach to risk estimation. As Park and Snee note³⁷

"The one-hit model and variations on it utilizing upper statistical limits (Gaylor and Kodell, 1980) represent a highly conservative approach to the extrapolation problem (Hoel, 1981). For example, a linear extrapolation of the Chemical Industries Institute for Toxicology formaldehyde study predicted that an average lifetime dose of less than 0.66×10^{-3} ppm was needed to keep the lifetime potential risk of tumor less than 10^{-6} (Gibson, 1982). Such an estimate has little credibility as an estimate of the risk to humans when viewed in light of about 100 years of experience with human exposures to formaldehyde that generally are less than 0.1 ppm but have often been in the 0.1 to 5 ppm range . . . with no apparent increased carcinogenic risk."

Indeed, these authors are quite specific about the limitations of one-hit models. Later, in this same paper, they state,

³⁶Maxim, L. Daniel, and Leigh Harrington, Everest Consulting Associates, Inc., "A Review of the Food and Drug Administration Risk Analysis for Polychlorinated Biphenyls in Fish," Regulatory Toxicology and Pharmacology, Volume 4, Number 2, June 1984, p. 212.

³⁷Park, C. N. and R. D. Snee, "Quantitative Risk Assessment: State-Of-The-Art For Carcinogens," American Statistician, Volume 37(4), 1983, pp. 247 et seq.

"With appropriate species conversion, the one-hit model does, however, estimate an upper limit on the potential risk and may be useful in situations where an upper bound is of interest. For example, if the potential risk calculated by the one-hit model is not unacceptable, then there would be less need to consider other models. On the other hand, if permissible exposures predicted by the one-hit model are unrealistically low, which is often the case, then further risk analyses would have to be made to confirm or refute the one-hit model results. In all cases we must keep in mind that potential risks predicted by the one-hit model may be several orders of magnitude more than that of the true potential risk (factor of 10 = one order of magnitude)." (Emphasis added)

Other researchers have also questioned the appropriateness if not the conservatism of the use of the one-hit model. In a report prepared for EPA by Midwest Research Institute (MRI), the one-hit model was challenged³⁸

"If mathematical extrapolation is used, the model(s) selected should meet at least three criteria: (1) it should be capable of fitting observed dose-response data for a wide range of chemicals if it is expected to have much credibility in extrapolations below the observed dose range; (2) it should be in agreement with (or at least not in disagreement with) our understanding of the mechanism of carcinogenesis; and (3) it should be useful with the kind of data sets likely to be available for chemicals typically found in hazardous wastes. These criteria appear to rule out use of the Mantel-Bryan and one-hit models. The models of choice seem clearly to be the multistage and the Weibull. Both have good flexibility in being fit to diverse data sets, and usually become essentially linear in low dose extrapolation. The multistage has been well regarded because of its rationale, utility, and "conservativeness." Its linearized version gives linear upper confidence limits on risk in extrapolation. On the other hand, opinions have been expressed that the multistage models estimate risks that are too high at low dose to serve as the primary basis of regulation (particularly when substantiating observations on humans are lacking). The fact that the linearized multistage model gives nearly the same estimates of low dose risk as the discarded one-hit model is a cause of substantial concern." (Emphasis added)

Other investigators have likewise argued against the one-hit model and have suggested alternative models.

These alternative models are equally or even more plausible than the one hit model.

³⁸Midwest Research Institute, Risk Assessment Methodology for Hazardous Waste Management, Draft Final Report, 31 July 1986, VI-67.

The one hit model used by FDA³⁹ specifically excludes the possibility of threshold effects. A threshold model is one in which little or no biological response occurs at doses beneath a threshold value. As a matter of "science policy" threshold models have not been employed by most regulatory agencies for carcinogens. However, the toxicological basis for this policy can be questioned, at least for some possible compounds.

As noted in the MRI report prepared for EPA,⁴⁰

"Belief that a threshold should not exist for carcinogens became a given in the so-called Delaney Clause of the 1958 Amendments to the Food, Drug and Cosmetics Act. Reconsideration of the range of biological origins of cancer have recently led to suggestions that threshold doses might exist for some carcinogens, but not for others. In particular, carcinogens that act through 'epigenetic' mechanisms (e.g., via formation of bladder stones) were viewed in one study as more likely to have threshold than those causing somatic mutations (genotoxic mechanisms), although the data were not conclusive (OTA, 1981). In 1985, however, an expert review (OSTP, 1985) noted that a chemical that only causes cancer secondarily to a gross physiological effect is likely to have a threshold at some dose level below that which causes the physiological effect."

Elsewhere in this testimony it is argued that threshold effects for PCBs are likely.

The existence of a threshold would radically alter the dose response analysis employed by FDA and, depending upon the threshold value, could dramatically reduce the estimated risk associated with consumption of PCB-contaminated fish.

- Lifetime Exposure to Non-Declining Levels of PCB

The FDA analysis assumed that persons would eat fish containing the same PCB levels throughout their entire lifetime. In fact, PCB levels in fish nationally have generally been declining, implying that lifetime health risks were overstated in the FDA analysis. If PCBs were to decrease with a half life of 6 years, the FDA overstatement of risk would be a factor of 7.

³⁹Alternative one-hit models have been proposed that incorporate threshold effects, but these were not employed by FDA.

⁴⁰Midwest Research Institute, Risk Assessment Methodology for Hazardous Waste Management, Draft Final Report, prepared for EPA, 31 July 1986, VI-II.

Of course, it may be argued that (notwithstanding the observed decrease in biologically active congeners in the Acushnet estuary discussed earlier) comparable declines have not been observed in the fish and shellfish in Buzzards Bay. Even assuming this to be true for purposes of argument, it does not follow that lifetime risks among present residents would be as high as calculated by FDA, because individual geographical mobility is such that it is unlikely that lifetime exposures would result. In a critique of conservative assumptions in exposure analysis, the Office of Management and Budget noted,⁴¹

"Lifetime exposure assumed. Risk assessments often also assume that humans are exposed for their entire lives (or working lives, often 45 years, in the case of occupational exposure) to a particular chemical from a particular source and under the worst-case environmental assumptions. For example, in its recent proposal to restrict land disposal of hazardous waste, EPA calculated the human risk on the basis of an individual who would drink 2 liters every day for 70 years from a contaminated groundwater well (this is in addition to many other highly cautious assumptions). Using these same assumptions, diet soda or beer would pose risks hundreds of times greater than the level EPA proposed for the contaminated water. OSHA often assumes that workers are exposed for 45 years - from age 20 to 65 - in estimating the number of cancers that would be avoided by regulation. Actually, Americans are highly mobile and unlikely to live in the same location or work at the same job for their entire lives. These assumptions can bias the estimates of risk upwards. Moreover, use of lifetime risk estimate incorrectly implies that the last year of exposure contributes as much to the individual's health risk as earlier years of exposure and the onset of cancer is often 20 years or more, exposure at age 60 would not be expected to manifest itself during a normal life expectancy." (Emphasis added)

Any reduction in the assumed exposure duration would, of course, involve a corresponding reduction in risk.

- Effects of Cooking

The FDA analysis was based upon the assumption that fish were either consumed raw or that preparation and cooking do not reduce PCB levels in fish and shellfish. As FDA acknowledged this assumption overstates the actual exposure,⁴²

⁴¹Executive Office of the President, Office of Management and Budget, Regulatory Program of the United States Government, April 1, 1986 - March 31, 1987, Washington, D.C., 1986, p. xxv.

⁴²Federal Register, Volume 42, Number 63, 1 April 1977 pp. 17493.

"Actual PCB intake can be considered to be even lower in light of a study of PCB levels in cooked fish. Most of the PCB occurrence data are for raw fish and comparisons of PCB levels in raw versus cooked fish indicate that actual human exposure to PCB's from fish consumption is less than might be expected from the raw fish data. This is not unexpected, because preparation (trimming away fatty tissue) and cooking have been shown to decrease the concentration of PCB's. For example, the PCB level in cooked lake trout ranged from 1.03 ppm to 4.67 ppm; in cooked coho salmon from 0.48 ppm to 5.38 ppm; and in other cooked fish from 0.36 ppm to 2.06 ppm. These levels are decidedly lower than the mean levels of 22.91 ppm and 10.45 ppm reported in raw lake trout and coho salmon, respectively, for 1974."

A comparison of the above data for raw fish with prepared and cooked fish suggests that risks could be overstated by a factor of as much as 10 or more just due to this one assumption.

- Basis For Animal To Human Extrapolation

FDA's calculation of risk given in Table 2 assumes that animals and humans face identical risk when fed a diet containing equal amounts of PCBs on a parts per million basis. Many investigators challenge this conversion and hold that the proper basis for comparison is on a dosage basis, i.e., a micrograms of PCBs per kilogram of body weight per day basis. In particular, the chairman of the very FDA task force that prepared the PCB risk analysis has apparently rejected the "parts per million-in-diet" approach employed in the original analysis in favor of a weight per kilogram of body weight per day basis! Again,⁴³ commenting on a similar EPA analysis, Rodricks stated, "Thus, in the absence of good evidence for the use of a more complex procedure, and because the available evidence appears to support it, EPA should use, mg/kg/day as the basis for interspecies dosage comparison." The consequences of this change in species conversion factor have been examined by Maxim and Harrington⁴⁴ and lead to a five- to eleven-fold reduction in estimated risk, depending upon the dose-response model chosen.

⁴³Rodricks, J., "A Review of EPA's Carcinogenic and Reproductive Assessments," in a report to CMA PCB Panel, Environ Corp., Washington, D.C., February 1984.

⁴⁴Maxim, L. Daniel, and Leigh Harrington, Everest Consulting Associates, Inc., "A Review of the Food and Drug Administration Risk Analysis for Polychlorinated Biphenyls in Fish," Regulatory Toxicology and Pharmacology, Volume 4, Number 2, June 1984, pp. 213-214.

- Lobsters Excluded

The original FDA analysis did not include lobsters, a significant omission with respect to this case. However, in response to comments on proposed rulemaking FDA did a separate analysis including lobsters, with the result that aggregate risks (above those given in Table 2) increased by less than 1.5%.⁴⁵ This result reflected the fact that lobster is not consumed in appreciable quantities in the average U.S. diet. It implies that even the FDA conservative calculations would lead to risks only 1.5% of those given in Table 2 for lobsters.

Conservative and Judgmental Aspects Acknowledged by FDA

The foregoing has indicated that, aside from lack of applicability of the FDA analysis in certain key respects, there are numerous uncertainties in the risk analysis used in support of the FDA tolerance level decision for PCBs. When faced with these uncertainties, FDA generally chose conservative assumptions which led to overestimates of risk.

The above characterization is not merely a "partisan" assertion. In various announcements in the Federal Register and other papers, FDA has clearly acknowledged these uncertainties and the judgmentally conservative character of their resolution. For example, in the background to its 1979 ruling⁴⁶ FDA stated,

"Hence, in deciding the appropriate levels for PCB tolerances under section 406, FDA had to make some extraordinarily difficult judgments. It has had to decide, in effect, where the proper balance lies between providing an adequate degree of public health protection and avoiding excessive losses of food to American consumers." (Emphasis added)

FDA noted that⁴⁷

⁴⁵Memo from Peng Tuli to Elizabeth J. Campbell, 21 April 1982 and part of the hearing record.

⁴⁶Federal Register, Volume 44, Number 127, 29 June 1979, pp. 38330 et seq.

⁴⁷Federal Register, Volume 44, Number 127, 29 June 1979, pp. 38331 et seq.

". . . it (FDA) also must make that judgment on the basis of data that are incomplete, or even in dispute, and that can easily lead reasonable people to different conclusions." (Emphasis added)

At the most basic level, uncertainties exist with respect to the carcinogenicity of PCBs in humans. FDA conceded this,⁴⁸

"FDA considers the question of the carcinogenicity of the PCB's unresolved. For the purposes of this risk assessment on PCBs, however, the agency treated the various PCBs as though they were carcinogenic and it considers the carcinogenicity of PCBs to be a matter worthy of further serious inquiry."

Having thus dealt with this key question by assumption, the FDA risk analysis proceeded to incorporate other conservative assumptions. These too, were explicitly acknowledged by FDA,⁴⁹

"The risk assessment the agency made incorporated several conservative assumptions that were designed to avoid understatement of the human risk. Thus, it is expected that the actual risk experienced by consumers of the 12 more heavily contaminated species covered by the risk assessment is less than that estimated. Moreover, the average consumer, who eats fish from a variety of freshwater and marine sources, will actually experience a far lower level of PCB exposure and a correspondingly lower degree of risk than those whose fish consumption is concentrated among the more heavily contaminated (predominantly freshwater) species," (Emphasis added)

a statement echoed elsewhere in the 1979 Federal Register notice,⁵⁰ e.g.,

"These risk assessment methods do not purport to quantify precisely the expected human risk, but rather attempt to estimate in quantitative terms an upper limit on the risk to humans that can be expected from a given level of exposure to a toxic substance, assuming humans are no more susceptible to the effects of the substance than are the most susceptible members of the animal species for which toxicity data are available. These risk assessments can be useful as a means of comparing risks at various exposure levels and illustrating the toxicological judgment that a reduction in exposure will reduce risk. Because of all the problems inherent in extrapolating from animal data to the expected human experience, however the numbers produced by a risk assessment must be interpreted cautiously: They are estimates of upper limits on risk and, though potentially useful for

⁴⁸Federal Register, Volume 44, Number 127, 29 June 1979, pp. 38338 et seq.

⁴⁹Federal Register, Volume 44, Number 127, 29 June 1979, pp. 38334 et seq.

⁵⁰Federal Register, Volume 44, Number 127, 29 June 1979, pp. 38332 et seq.

comparative purposes, cannot be said to quantify actual human risk precisely. These assessments attempt to avoid underestimating human risk . . ." (Emphasis added)

and again in this same FDA document,⁵¹

"As explained in the report (Ref. 45), the utility of this risk assessment for evaluating actual risk to humans from exposure to PCB's is extremely limited. This is due both to difficulties inherent in making such extrapolations from animals to humans and, perhaps more importantly in this instance, to gaps and uncertainties in the data available for this particular risk assessment. For example, the toxicity studies on which the risk assessment is based used commercial preparations of PCB's, which are chemically different from the PCB residues found in fish and which contain small amounts of highly toxic impurities (e.g., dibenzofurans) not known to be present in fish residues. Also, in making the exposure estimates required for the risk assessment, it was necessary to use existing data on the numerical distribution of PCB levels in fish and rely on the assumption that the effect of a given tolerance level is to remove from commerce all fish containing PCB's exceeding the tolerances. It is possible that neither the assumption nor the data precisely reflect what actually occurs.

For these reasons and others discussed in the report (Ref. 45), the risk assessment does not provide a basis for precise quantification of the amount of risk reduction accomplished by reducing the fish tolerance."

These forthright statements by FDA lend important perspective to the resulting tolerance level decision. At issue here are two points:

- (i) Is such conservatism appropriate in the risk analysis process?
- (ii) What is the relevance of such a judgment-laden and conservative analysis to the question of actual (as opposed to theoretical upper-bound) natural resource damages to the Acushnet estuary and New Bedford Harbor?

The following sections explore the first of these questions.

Consequences of Conservatism in Risk Analysis: A Policy Perspective

The above discussion has indicated that the FDA standard was based upon a risk analysis employing numerous conservative assumptions, models, and inputs. As noted, it is unlikely that actual risks associated with consumption of PCB-contaminated fish or shellfish are even close to those calculated by FDA. If, indeed, the health risks shown in

⁵¹Federal Register, Volume 44, Number 127, 29 June 1979, pp. 38333 et seq.

Table 2 corresponding to the 2 ppm tolerance level can be judged acceptable, then the PCB levels corresponding to these risks are perhaps orders of magnitude larger than 2 ppm level and there can be no serious question of natural resource damages.

Other Federal agencies (e.g., EPA, OSHA) have also employed conservative inputs and models for calculating health risks (particularly cancer risks) associated with chemicals or hazardous wastes. In this sense, the conservative choices employed by FDA cannot be said to be unprecedented. The fact remains, however, that the FDA risk estimates are unrealistic, and arguably greatly so. Moreover, there is a growing awareness within the regulatory community that,

- (i) conservative assumptions can significantly overstate risks,
- (ii) such overstatement is ultimately counterproductive, and
- (iii) more realistic risk models are appropriate.

Table 3 presents an assembly of pointed quotes from regulatory personnel, environmentalists, and academics that address uncertainty, conservatism, and resulting consequences in calculating health risks.

As indicated by these quotes, modern thinking is shifting away from the "better safe than sorry" premise to endorse the development of models that more accurately portray the actual risks. The place for conservatism (if at all) should be in the risk management rather than the risk analysis phase of regulatory action. Indeed, "improving coordination and consistency in risk reduction" was one of the principal themes in the recent Executive Office of the President, Office of Management and Budget (OMB) 1986-1987 Regulatory Program.⁵² OBM was strongly critical of the conservative assumptions often employed in carcinogen risk and exposure assessment (see Table 4), and highlighted the reasons why such practices were flawed,⁵³

⁵²Executive Office of the President, Office of Management and Budget, Regulatory Program of the United States Government, April 1, 1986 - March 31, 1987, Washington, D.C., 1986.

⁵³Federal Register, Volume 49, Number 100, 22 May 1984, p. 21514.

**TABLE 2.
UPPER CONFIDENCE LIMITS (99%) ON LIFETIME RISKS OF CANCER
IN EATERS OF FISH SPECIES OF INTEREST, AS CALCULATED BY FDA**

Study	Basis parameter/species	Lifetime risks per 100,000 ^a							
		50th percentile eaters				90th percentile eaters			
		No assumed tolerance	Assumed tolerance			No assumed tolerance	Assumed tolerance		
			5 ppm ^b	2 ppm	1 ppm		5 ppm	2 ppm	1 ppm
NCI	Total malignancies (male and female rats)	4.1	3.7	2.7	1.6	10.6	9.8	7.2	4.4
NCI	Liver carcinoma and adenomas (male and female rats)	0.9	0.9	0.6	0.4	2.5	2.3	1.7	1.0
NCI	Hematopoietic (male and female rats)	2.7	2.4	1.8	1.1	7.0	6.5	4.7	2.9
Kimbrough	Liver carcinoma	1.3	1.2	0.8	0.5	3.4	3.1	2.3	1.4
Kimbrough	Liver Hepatomas (mice)	2.0	1.8	1.2	0.8	5.2	4.8	3.5	2.2

Source: Cordle, R. Locke, and J. Springer (1982), "Risk Assessment in a Federal Regulatory Agency: An Assessment of Risk Associated With the Human Consumption of Some Species of Fish Contaminated with PCBs," Environmental Health Perspectives, Volume 45, pp. 177-182.

^aAll risks are lifetime risks computed as rates per 100,000 of the population at risk.

^bFor each assumed tolerance, PCB values above the tolerance were eliminated.

TABLE 3.
UNCERTAINTY, CONSERVATISM, AND RESULTING CONSEQUENCES IN RISK ANALYSIS

QUOTE	REFERENCE
<p>"Historically at EPA it has been thought prudent to make what have been called conservative assumptions; that is, our values lead us, in a situation of unavoidable uncertainty, to couch our conclusions in terms of a plausible upper bound. This means that when we generate a number that expresses the potency of some substance in causing disease, we can state that <u>it is unlikely that the risk projected is any greater.</u></p> <p>This is fine when the risks projected are vanishingly small; it's always nice to hear that some chemical is not a national crisis. <u>But when the risks estimated through such assessments are substantial, so that some action may be in the offing, the stacking of conservative assumptions one on top of another, becomes a problem for the policymaker.</u> If I am going to propose controls that may have serious economic and social effects, I need to have some idea how much confidence could be placed in the estimates of risk that prompted those controls. I need to know how likely total damage is to occur in the uncontrolled, partially controlled, and fully controlled cases. Only then can I apply the balancing judgments that are the essence of my job." (Emphasis added.)</p>	<p>Ruckelshaus, W. D. (former EPA Administrator), "Risk in a Free Society," <u>Risk Analysis</u>, Vol. 4, #3, 1984, pp. 157 <u>et seq.</u></p>
<p>"I'm skeptical of quantitative risk assessment, at least in the cancer field. The science is too imperfect, and the results are likely to be used literally, because all the caveats get lost."</p>	<p>Ahmed, K. (Research Director for the Natural Resources Defense Council), as quoted by B. Barker, "Cancer and the Problems of Risk Assessment," <u>EPRI Journal</u>, December 1984, p. 30.</p>
<p>.. "Milton Russell, Assistant Administrator for Policy, Planning, and Evaluation at EPA, added that 'depending on which animal you use, and whether you use a model that uses surface area or weight, you can get a difference in risk of up to 39,000 times.' He went on to add that uncertainties in the risk assessment process are multiplied (not added) and in the case of cancer risk this leads to extreme conservatism in the decision-making process. 'If you are relatively sure of the probability of risk, like automobile accidents, the range of uncertainty is narrow, and the difference between a plausible upper bound and a maximum likelihood and a plausible lower bound is relatively small. But if you are quite uncertain (as we are in many of these health effects), the range between this upper and lower bound is very, very large. <u>Multiplying the large uncertainties associated with each factor in the estimate leads to cascading conservatism in decision making.</u>' (Emphasis added.)</p>	<p>Barker, B., "Cancer and the Problems of Risk Assessment," <u>EPRI Journal</u>, December 1984, p. 30.</p>

TABLE 3.
UNCERTAINTY, CONSERVATISM, AND RESULTING CONSEQUENCES IN RISK ANALYSIS
 (continued)

QUOTE	REFERENCE
<p>"Often each conservative assumption is made by a different scientist or analyst responsible for a portion of the risk assessment. Each may think that erring on the side of caution or conservatism is reasonable. However, the effect of these individual conservative assumptions is compounded in the final estimate of risk presented to the decisionmaker. For example, if at each of two different steps in an analysis, estimates are chosen that have a 5 percent chance of being less than the true risk, then the final risk estimate will have only a 0.25 percent chance of being less than the true risk ($0.05 \times 0.05 = 0.0025$). That is, the risk estimate will have a 99.75 percent chance of being greater than the true risk. If there were 5 steps in the analysis instead of 2 and a conservative estimate at the 5 percent level were chosen for each step, then the final risk estimate would have a 0.00003 percent (0.05^5) chance of being less than the true risk, or 3 chances in 10 million. In other words, the estimate has a 99.99997 percent chance of overstating the true risk.</p> <p>In practice, there may be as many as 20 distinct stages in a risk assessment where conservative assumptions are made. A typical risk assessment would probably contain about 10. The final risk estimate derived from these compounded conservative assumptions may be more than a million times greater than the best estimate and may, thus, have a probability of being accurate, that is virtually zero. Some combinations of these highly cautious assumptions so overstate the risk that they are unrealistic."</p>	<p>Executive Office of the President, Office of Management and Budget, <u>Regulatory Program of the United States Government, April 1, 1986 - March 31, 1987</u>, Washington, D.C., pp. xxv, <u>et seq.</u></p>
<p>... "More recently, EPA has adopted the multi-stage model which has a linear component at low doses (4). This model assumes that cancer is caused by a series of mutational steps, whose occurrence rest both on dose and potency. This model also results in a conservative estimate. Most scientists accept these models as giving plausible upper limit estimates for a chemical's potency at low levels of exposure. <u>In other words, the potency of a substance is unlikely to be higher than that estimated using the linear model, but could be substantially lower. Use of the linear non-threshold models reflects EPA's decision to err on the side of caution in the face of uncertainties. The final result of the linearized extrapolation is a 'unit-risk factor,' which gives the estimated upper limit lifetime risk per unit of exposure.</u>" (Emphasis added.)</p>	<p>Patrick, D. R. (EPA), "Environmental Protection Agency's Risk Management Policy," <u>Environmental Progress</u>, Vol. 4, #1, February 1985, pp. 20-22.</p>

TABLE 3.
UNCERTAINTY, CONSERVATISM, AND RESULTING CONSEQUENCES IN RISK ANALYSIS
 (continued)

QUOTE	REFERENCE
<p>"These gaps in our scientific understanding and data limitations imply that it is difficult to conduct a good risk assessment. It is no surprise that they vary in quality. The many stages where judgment must be applied make it very easy for the results to substantially overestimate or underestimate the unknown true risks. <u>Because a government agency's mandate typically is to protect the public, or to be safe rather than sorry, the cumulative effect of these conservative assumptions may be very large. The resulting risk estimates often are treated as plausible upper bounds. Unless the uncertainty associated with each assumption is stated, risk managers often view these risk estimates as actual risks.</u>" (Emphasis added.)</p>	<p>Fisher, A. (EPA), "Using Risk Assessments in Policy Decisions," draft EPA document, 1986, p. 13-14.</p>
<p>"The Agency is not alone in its concern that different assumptions and different mathematical models used can significantly alter the outcome of risk assessment. When the Occupational Safety and Health Administration (OSHA) published its cancer policy in 1980, it did detailed comparisons of how estimates of carcinogenic risk can vary with the assumptions used in developing the estimates (45 FR 5198-5200). By varying the method of low dose extrapolation used, and the toxicology or epidemiology study which formed the basis of the risk assessment commenters to the OSHA policy developed risk estimates for exposure to 1 ppm of vinyl chloride which ranged from 10^{-8} (one in one hundred million) to 10^{-1} (one in ten, or 10%). A similar exercise with saccharin by NAS, and reprinted in the OSHA policy (45 FR 5200), estimated the expected number of cancer cases in the general population (exposed at 0.12 grams/day) at between 0.001 cases per million exposed, and 5200 cases per million exposed. These differing estimates were developed by using different low-dose extrapolation models and different animal-to-human extrapolation methods — all of which had some credence in the scientific community."</p>	<p>United States Environmental Protection Agency, <u>Risk Assessment: Framework for Decision Making</u>, EPA 600/9-85-002, December 1984, p. 16.</p>
<p><u>"Probabilistic reports should not prejudice policy issues and purposely report with a prudent bias. Cascading prudent reports could result in imprudent actions, and there is a danger of double-counting competing risks. Such reporting should be honest, and not attempt to second-guess policy choices. Probabilistic reports about diverse consequences to health, for example, are very often slanted to be conservative. I believe that it is better to report honestly, and that prudence should, more appropriately, be accounted for in the evaluation process, rather than in the assessment process."</u> (Emphasis added.)</p>	<p>Raiffa, H., "Science and Policy: Their Separation and Integration in Risk Analysis," <u>The Risk Analysis Controversy: An Institutional Perspective</u>, Springer-Verlag, Berlin, Heidelberg, New York, H. C. Kunreuther and E. V. Ley, editors, 1982, pp. 32-33.</p>

TABLE 3.
UNCERTAINTY, CONSERVATISM, AND RESULTING CONSEQUENCES IN RISK ANALYSIS
 (continued)

QUOTE	REFERENCE
<p>"Recent research has also shown a need to reevaluate the role of 'conservatism' in assessing and managing risk. Making a 'conservative decision' (i.e., one that is likely to be more protective of health and the environment than an alternative decision) is widely accepted as a prudent practice in risk management. <u>In keeping with the recommended separation of risk assessment and risk management activities, however, conservative assumptions, conservative models, conservative estimates, etc., should not be key elements in the science-based risk estimation steps. A catenation of conservative assumptions, models, and estimates throughout a risk assessment can lead to a worst-case' (or even worst-of-the-worst-cases) prediction that may be of little value (or possibly misleading) to the decision maker.</u> Most decisions actually involve 'either-or' choices between technological alternatives with different risk levels rather than a 'yes-no' choice on a single risk. When dissimilar alternatives require different analysis procedures, conservatism ambiguously or inconsistently applied could lead to biased results and poor decisions — even to the choice of a technology that is less protective of human health and the environment and possibly more costly to society than an available alternative. Best estimates of the risks, costs, and benefits for the alternatives, coupled with consideration of their uncertainties (including worst-credible case considerations), should produce the optimal basis for decision making. The Council on Environmental Quality has recently noted that 'rules of reason' should replace worst case analysis as the basis of regulatory decision making (CEQ, 1985, 1986)."(Emphasis added)</p>	<p>Midwest Research Institute, <u>Risk Assessment Methodology For Hazardous Waste Management</u>, Draft Final Report, prepared for EPA under Contract No. EQ4C15, 31 July 1986.</p>

TABLE 4.
OMB CHARACTERIZATION OF CANCER ASSESSMENT MODELS
EMPLOYED BY EPA AND OTHER FEDERAL AGENCIES

"A few examples of these cautious or conservative assumptions are: (1) treating all benign tumors as malignant, (2) using data about only the most sensitive animal species and sex, and (3) using conservative mathematical models to extrapolate from high to low doses. Each of these three kinds of assumptions is discussed briefly below.

All benign tumors treated as malignant. In interpreting animal studies, agencies frequently interpret both benign (noncancerous) tumors and malignant (cancerous) tumors to be equally strong indications that a substance is a carcinogen. Scientists know, however, that not all benign tumors evolve into malignancies. Studies that treat benign tumors the same as malignant tumors can overstate the real risk present. Some risk assessments based on animal studies have concluded that a chemical is carcinogenic solely because of an increased number of benign tumors. Assuming that all benign tumors will become malignant will not produce a best estimate of the risk.

Use of most sensitive species and sex. Even though the results of several animal studies may be available for a particular suspected carcinogen, it is not unusual for the risk estimate to be derived only from the data for the most sensitive exposed species and sex. This conservative approach tends to overpredict the risk to humans, because it assumes that humans are as sensitive as the most sensitive animal tested even when the most sensitive animal tested is hundreds of times more sensitive than any other animal tested. Furthermore, by using the same data to derive the risk estimate and to determine the most sensitive species, the chance is increased that statistical anomalies will lead to overestimates of the risk. (If a statistical anomaly causes an upward bias in the estimated risk for a particular species, it will also increase the chance that that species will be selected as the most sensitive.) A more accurate estimate could be derived from a weighted average of all the scientifically valid, available information.

Conservative extrapolation from high doses to low doses. To determine the risks to humans from exposure to a substance, scientists must extrapolate (or estimate) from the results of high doses in animal experiments to the comparatively low doses of human exposure. This extrapolation relies upon statistical models. The risk from exposure to low doses cannot be determined with certainty. In making the extrapolation, the common practice is not to make a best estimate of the risk from human exposure to low doses, but to determine what a maximum risk would be. Often, such an extrapolation has a 95 percent chance of overstating the true risk. Usually, the explanation for using these conservative assumptions is to ensure that the actual risk is not underestimated. However, the resulting risk estimate can be over one hundred times greater than the best estimate of the risk."

Source: Executive Office of the President, Office of Management and Budget, Regulatory Program of the United States Government, April 1, 1986 - March 31, 1987, Washington, D.C., p. xxiv.

"Risk Assessments with such extreme conservative biases do not provide decisionmakers with the information they need to formulate an efficient and cost-effective regulatory strategy. Furthermore, the inconsistency of these assumptions makes it virtually impossible to compare risks from different sources. It is particularly difficult to compare safety risk estimates, which are usually best estimates, with health risk estimates, which usually are not best estimates, because the latter embody a series of conservative assumptions. Even different estimates of health risks may not be comparable because of the different degrees of conservatism built into them. Where risk estimates for two different risks cannot be compared, it will be impossible to compare the effects of regulations controlling them.

A perverse and unfortunate outcome of using upper-bound estimates based on compounded conservative assumptions is that it may lead us to regulate insignificant risks and ignore more serious risks. Furthermore, the more uncertain we are about the risk posed by a particular hazard, the higher the upper-bound risk estimate will be. Therefore, the less information we have on the risk posed by a potential hazard, the more likely we are to regulate it. Other hazards that pose certain but smaller risks are not considered as dangerous and may not be regulated. Yet, hazards with better understood risks may be more serious.

All the problems we have discussed resulting from compounding conservative assumptions can be addressed by developing best estimates at each stage of the risk assessment process. Estimates of the uncertainty and the outer ranges of potential risk can be developed to supplement the best estimate. Both the best estimate and these supplementary risk indicators should be made available to decisionmakers. Then, if regulatory decisionmakers want to choose a very cautious strategy of risk control, they could do so and a margin of safety could be applied at the final decision and would be based on all the available information about its consequences and those of alternative strategies. The public and affected parties would also benefit from knowing both the expected risk and the margin of safety rather than being given only alarming and inconsistent estimates that are likely to be very different from actual risks.

Only when best estimates of risks and other information on the likely level of risks are presented to the decisionmaker, rather than hidden in the assumptions, can we be sure that we are issuing regulations that will make society as well off as possible. Fortunately, more review by regulating departments and agencies and by the Executive Branch has already begun to improve consistency in risk assessment and risk management and, thereby, improve societal welfare. Executive Order No. 12291 provides a mechanism to help ensure consistency." (Emphasis added.)

Seen in this perspective, the conservative assumptions used by FDA in setting PCB tolerance levels in fish are potentially counter-productive rather than simply "prudent."

An Important Aside: FDA's Legislative Mandate and Its Consequences

It is also important to bear in mind the statutory framework under which FDA establishes PCB limits for fish and other foods sold in interstate commerce. As FDA notes,⁵⁴

"Section 406 of the Federal Food, Drug, and Cosmetic Act ('the act'), 21 U.S.C. 346, authorizes the establishment of tolerances for poisonous or deleterious substances added to food that cannot be avoided by good manufacturing practice. PCBs are such a substance. Although the agency's paramount concern is protection of the public health, under section 406 the agency must consider, in establishing a tolerance, the extent to which a contaminant is unavoidable. In essence, the agency is permitted to find where the proper balance lies between adequately protecting the public health and avoiding excessive losses of food to American consumers. 44 FR 38330-31." (Emphasis added.)

Put somewhat differently, tolerance levels are established at a level "appropriate to protect the public health" or to "provide an adequate degree of public health protection." But tolerances established by FDA also reflect existing levels of contamination and the extent of its "avoidability" in food products to be regulated.

On first reading, the "balancing provisions" of Section 406 of 21 USC 346 appear quite reasonable. But, on more careful examination, there are curious, and arguably preverse, consequences resulting from how this legislative mandate is interpreted by FDA.

Consider, for example, two hypothetical foodstuffs, A and B, each contaminated initially to an identical degree with the same hazardous substance,

- (i) in product A, the contamination levels are expected to remain constant over time, but
- (ii) in product B the levels of contamination are expected to decline in the future.

Assuming that products A and B are consumed in equal amounts in the human diet, are absorbed equally, etc., the lifetime incremental health risks associated with consumption of product B are obviously smaller. Product B, by any objective standard, presents less

⁵⁴Federal Register, Volume 49, Number 100, 22 May 1984, p. 21514.

of a health hazard than product A. Yet, there is no guarantee that FDA tolerance levels for the hazardous contaminant in product B will be larger than, or even the same as, those for product A. In fact, quite the reverse is likely to be true. This is because the risks associated with product B became progressively more "avoidable" over time -- a phenomenon that allegedly justifies lower tolerance levels.

The above situation is by no means hypothetical, it has occurred with respect to PCBs in poultry and fish. In 1977,⁵⁵ the FDA proposed a reduction in the tolerance level for PCBs in poultry (later implemented) from 5 ppm (fat basis) to 3 ppm (fat basis), not because PCBs were thought to be more dangerous, but rather because elevated PCB levels were infrequent and declining in poultry:

"Because the frequency of PCB residue occurrence in feeds is low, the likelihood of residues in poultry reaching the 3 ppm (fat basis) level is very small. Moreover, data regarding PCB residues in poultry confirm this and show that PCB contamination of poultry is very sporadic and infrequent. As such, this food is not a significant source of dietary PCBs. A tolerance of 3 ppm (fat basis) will continue to provide this assurance, while also providing adequate protection for the consumer. Therefore, the Commissioner proposes to reduce the temporary tolerance for poultry from 5 ppm to 3 ppm (fat basis). As stated previously, the finished feed tolerance of 0.2 ppm cannot be reduced at this time because the analytical methodology necessary to enforce a lower tolerance is not available. The Commissioner advises that when such methodology becomes available so that the 0.2 ppm feed tolerance can be reduced, the tolerance for PCB residues in poultry will also be reevaluated."

Likewise, with respect to fish, FDA concluded that declining PCB levels were a reason for reducing tolerances;⁵⁶ "Based on the declining incidence of PCB contamination, which means that PCBs are now avoidable in food to a greater degree now than they were earlier . . . FDA decided the PCB tolerances should be reduced." Later in this same document, in response to the comment that PCB levels in fish were declining, FDA reaffirmed its proposed standard, noting;⁵⁷ "Moreover, that PCB levels

⁵⁵Federal Register, Volume 42, Number 63, 1 April 1977, pp. 17491-17492.

⁵⁶Federal Register, Volume 44, Number 127, 29 June 1979, p. 38331.

⁵⁷Federal Register, Volume 44, Number 127, 29 June 1979, p. 38337.

Thus, the FDA final decision in 1984 to lower tolerance levels in fish from 5 ppm to 2 ppm has to be interpreted very carefully, not only because it is based on conservative assumptions, as noted above, but also because of the particular legislative mandate under which it was conducted. Put simply, a reduction of the tolerance level may reflect declining environmental PCB levels rather than emerging knowledge with respect to health hazards of this chemical.

Summary

This discussion has demonstrated that the FDA risk analysis is likely to significantly overstate the health risks associated with consumption of PCB-contaminated fish and shellfish. The extent of this overstatement could be several orders of magnitude.

Whatever its merits in a policy context, the FDA tolerance level has little to do with actual risks of eating PCB-contaminated fish and shellfish from New Bedford Harbor.