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INTRODUCTION

In 1976, after five years of debate, Congress enacted the Toxic Substances Control Act (TSCA).[1] TSCA expands existing federal authority to regulate the chemical industry by granting to the Environmental Protection Agency (EPA) the authority to compel testing of chemicals and to regulate their production, use, and disposal. The House Report in support of the bill states that "the overriding purpose of the bill is to provide protection of health and the environment through authorities which are designed to prevent harm."[2] The House Report also states that Congress' concern was generated by the "vast volume" of chemicals, which have become a "pervasive and enduring part of our environment," and "have, for the most part, been released into the environment with little or no knowledge of their long-term health or environmental effects."[3]

Simply put, the purpose of the Act is to prevent harm. This broad goal will not be met, however, if in administering the Act EPA does not develop a regulatory scheme that is responsive to the immense task of regulating thousands of chemicals. Preventing harm before it emerges requires a regulatory system that is based on prediction of risk. Unfortunately, past attempts to regulate significant economic activity on the basis of predicted risks or costs to the environment or to health have failed, as evidenced by

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1. Pub. L. No. 94-469, 90 Stat. 2003 (codified at 15 U.S.C.A. §§ 2601-2629 (West Supp. 1976)).

2. H.R. REP. NO. 1341, 94th Cong., 2d Sess. 7 (1976).

3. *Id.* at 3.

the experiences with pesticides, food additives, and hazardous substances. Similar attempts to control economic activity under the National Environmental Policy Act[4] also have failed. Unlike earlier statutes, TSCA takes major steps towards changing this situation, by requiring advance testing of, and by placing added burdens on, "new" chemicals and new uses of "old" chemicals. Of equal importance, TSCA gives EPA an opportunity to depart from the traditional modes of regulation by authorizing the control of toxic substances according to categories of chemicals.

Categorization of chemicals is a method through which scientists can infer which chemicals present risks of harm to humans and to the environment. Many different categorization schemes are possible. Chemicals can be classed on the basis of their scale of production,[5] type of use,[6] or physical, biological, and chemical properties. They can be classed according to known or possible effects such as carcinogenicity, mutagenicity, and teratogenicity, all of which are special concerns under TSCA. The results of screening tests can also be the basis for categorization. For instance, categories could be established for chemicals which have positive Ames tests,[7] an indicator of mutagenicity and carcinogenicity, or which have high partition coefficients, an indicator of a tendency to bioaccumulate.[8]

When there may be little or no specific information about a substance, a categorization scheme based on structure-activity relationships offers EPA a way of predicting with substantial, but not absolute, reliability the expected threat that a compound may present. Under such a scheme, EPA can make inferences about the toxicological properties of one compound based on those which are known about another.

This Article proposes, as an approach to chemical regulation under TSCA, the adoption of a regulatory scheme which uses categorization as its primary mode of determining potential harm. Among the different methods of classifying chemicals, the Article focuses on categorization schemes based on structure-activity relationships. This approach, where scientifically justified, is consistent with the congressional purpose of preventing harm to humans and the environment.

This Article is divided into five sections: section I examines the inadequacies of existing modes of chemical regulation; section II analyzes the statutory authority to regulate chemicals by category under TSCA; section III discusses the scientific basis for categorizing chemicals according to structure-activity relationships; section IV explores the legal sufficiency

4. 42 U.S.C. § 4321 (1970).

5. Scale of production is important because chemicals manufactured or processed in large quantities tend to become ubiquitous, and therefore may present great potential dangers if they later are found to be toxic.

6. Uses which expose humans directly to a chemical obviously present greater risks than uses for which there is no human contact.

7. See text accompanying note 19 *infra*. See also note 112 *infra*.

8. See note 20 *infra*.

of the scientific hypothesis underlying a category for purposes of applying the substantial evidence test; and section V explains the various ways categorization may be used to facilitate the administration of the Act.

I

INADEQUACIES OF EXISTING MODES OF CHEMICAL REGULATION

Regulation of chemicals is a complex and difficult task, primarily because of the enormous number of chemicals in the marketplace. In 1975, the United States produced a total of 155 billion pounds of 8,000 different synthetic organic chemicals, for a value of nearly $25 billion.[9] Although the production of synthetic organic chemicals constitutes the largest sector of the chemical industry, it is only one part of the industry. Altogether, approximately 63,000 different chemical compounds are currently in commerce.[10]

The chemical industry introduces approximately 3,200 new or grossly modified substances each year.[11] In addition, thousands of other chemicals are produced as intermediates, impurities, and by-products. Although these numbers are substantial, they are but a small fraction of the more than four million unique chemicals catalogued by the Chemical Abstract Service.[12]

Many of these chemicals exhibit toxic properties. The latest edition of the toxic substances list published by the National Institute for Occupational Safety and Health (NIOSH) includes 21,729 different compounds for which some type of toxicological information is available.[13] The NIOSH editors estimate that there are about 100,000 chemicals for which some information about toxic effect may be available.[14] Not all of these chemicals are produced commercially.

The problem presented by the sheer number of chemicals is exacer-

9. U.S. INT'L TRADE COMM., SYNTHETIC ORGANIC CHEMICALS, U.S. PRODUCTION AND SALES, 1975, at 3 (1977). These statistics include only those chemicals for which sales have exceeded 1,000 pounds or whose sales value was greater than $1,000 per year.

10. Maugh, *Chemicals: How Many are There?* 199 SCIENCE 162 (1978). Under § 8(b)(1) of TSCA, EPA must "compile and keep current, and publish a list of each chemical substance which is manufactured or processed in the United States." 15 U.S.C.A. § 2607(b)(1) (West Supp. 1977). The list will exclude those chemicals which are manufactured or processed only in small quantities for research and development. Congress originally intended the inventory to be published by November 1977. Publication is now scheduled for early 1979.

11. MANUFACTURING CHEMISTS ASSOCIATION, STUDY OF THE POTENTIAL ECONOMIC IMPACTS OF THE PROPOSED TOXIC SUBSTANCES CONTROL ACT AS ILLUSTRATED BY SENATE BILL S. 776, at 6 (1975) [hereinafter cited as MCA TSCA STUDY]. This number is also approximate; it is difficult to find reliable information on the introduction of new chemicals into the marketplace.

12. Maugh, *supra* note 10, at 162.

13. NAT'L INSTITUTE FOR OCCUPATIONAL SAFETY & HEALTH, DEP'T HEALTH, EDUCATION & WELFARE, REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES, 1976 EDITION (1976).

14. *Id.* at v. Of course, the costs imposed by a given compound are dependent on its scale of production, use, type and extent of exposure, affected population, and possible synergistic relationships with other chemicals.

bated by the fact that each substance can have multiple harmful effects on humans and the environment. For example, nitrogen oxides, which are believed to contribute to chronic respiratory disease, also are believed to contribute to atmospheric reactions leading both to the formation of photochemical smog and to the depletion of the ozone layer.

Testing methods currently in use are proving to be inadequate in light of the large number of chemicals subject to control and the myriad toxic effects of each. Traditional full scale animal testing as the sole predictor of harm is ineffective for several reasons. The focus of an animal test usually is narrow, and therefore may not reveal toxic effects it is not designed to detect. The costs of such tests are high, in terms of both time and money. A long-term study of the effects of a single chemical on laboratory animals may take three years and may cost more than a quarter of a million dollars.[15] In 1974, only 500 compounds were tested for toxicological properties,[16] and the Manufacturing Chemists Association estimates that it would take three to five years to double the existing capacity for toxicological testing.[17]

Quicker tests, such as the Ames test, cited in the House Report,[18] also have limitations. The Ames procedure tests for mutagenicity as a surrogate

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15. MCA TSCA STUDY, *supra* note 11, at 126. Theodore L. Cairns, the Director of Du Pont's Central Research and Development Department, testified during the hearings on TSCA that:

> A typical testing program might include one or more of a number of different toxicity test programs of varying complexity and duration. All of these tests require professionally trained scientists with appropriate support personnel, take from 30 days to several years to complete, and are quite costly. . . . It is possible to spend more than 4 years and more than $500,000 to complete the various oral, dermal, inhalation and other special tests that could be required for just one chemical substance.

Toxic Substances Control Act: Hearings on H.R. 7229, H.R. 7548, and H.R. 7664 Before the Subcomm. on Consumer Protection and Finance of the House Comm. on Interstate and Foreign Commerce, 92nd Cong., 1st Sess. 287 (1975). *See also* Exhibit A appended to the Cairns statement, which estimates the costs and times for completion of various types of chronic and acute toxicity tests.

The costs of chemical testing are a controversial subject and estimates vary widely. Costs depend on the degree and extent of the testing program. *See Toxic Substances Control Act: Hearings on S. 776 before the Subcomm. on the Environment of the Senate Comm. on Commerce*, 94th Cong., 1st Sess. 98-102 (1975) (Report of the U.S. General Accounting Office).

16. MCA TSCA STUDY, *supra* note 11, at 138. The precise nature and extent of the testing of the compounds is not clarified.

17. *Id.* at 142.

18. "[T]he salmonella test developed by Dr. Bruce Ames of the University of California, Berkeley, . . . is now available for screening for cancer-causing properties of chemicals and . . . has considerably reduced both costs and time required for such screening." H.R. REP. No. 1341, 94th Cong., 2d Sess. 5 (1976). David Rall, the Director of the National Institute of Environmental Health Sciences, testifying to a Senate subcommittee investigating the PBB catastrophe in Michigan, said:

> How do we prevent future episodes? Environmental toxicology is much more complex than the simple testing of each compound to demonstrate whatever health effects it may have. It takes three to four years, a half million to a million dollars, and very importantly, one to two man-years of very scarce professional time just to test one compound. Since there are at least 10,000 compounds in the environment, and about a thousand new compounds added each year, this task on a chemical-by-chemical basis is impossible. We must develop broad concepts of toxicology that will permit us to

for carcinogenicity, based upon the hypothesis that a chemical which is mutagenic is also carcinogenic, *i.e.*, a chemical which causes mutations in bacteria can cause cancer in animals and humans.[19] Although the Ames and other such screening tests are fast, simple, reproducible, and cheap, their value as overall indicators of toxicity remains limited. Quick tests are still in their infancy, and there are many more toxic effects than there are methods for testing them.[20]

Another unsatisfactory method for detecting "potential" harm is reliance on persons exposed to hazardous chemicals. The practice of using the work force or other identifiable groups as accidental detectors of the toxicological properties of chemicals leads to unnecessary injury and loss of life, and is the problem to be solved—not a solution. The House Report cites the after-the-fact detective work on vinyl chloride, asbestos, and polychlorinated biphenyls (PCB's) as failures of the prior regulatory system.[21] To date, however, this detection method dominates, with most chemicals regulated on the ground that they cause occupational-linked illness. Examples include vinyl chloride, asbestos, and benzene.

Regulation based on after-the-fact information is unwise for other reasons. On the one hand, when harm has become apparent, public outrage or fear can force immediate action to control the perceived source of the problem. This response to environmental disasters leads to a climate of uncertainty and unpredictability. The sudden banning or stringent abatement of a chemical can cause economic dislocations. On the other hand, the public may suffer when a cautious approach takes the place of immediate regulatory action in an effort to protect existing jobs and economic commitments.

Many federal statutes contain provisions to regulate toxic substances. The Clean Air Act Amendments and the Federal Water Pollution Control Act Amendments (FWPCA) authorize the control of hazardous air[22] and water[23] pollutants. Similar regulatory provisions are found in the Federal

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design rapid specific screening tests, which will permit us to identify those relatively few chemicals that cause serious toxicity.

Toxic Substances: Hearings Before the Subcomm. on Science, Technology, and Space of the Senate Comm. on Commerce, Science, and Transportation, 95th Cong., 1st Sess., Part 1, 163-64 (1977) [hereinafter cited as 1977 *Toxic Substances Hearings*]. *See also* Bridges, *Short Term Screening Tests for Carcinogens*, 261 NATURE 195 (1976).

19. *See* Kolata, *Chemical Carcinogens: Industry Adopts Controversial "Quick" Tests*, 192 SCIENCE 1215 (1976); Edsall, 189 SCIENCE 174 (1975) (letter); Ames, McCann, & Sawyer, 194 SCIENCE 132 (1976) (letter). *But see* Sivak, 193 SCIENCE 272 (1976) (letter).

20. In addition to quick carcinogenicity tests, partition coefficients show promise, as predictors of chemicals which bioaccumulate. Chiou, Freed, Schmedding, & Kohnert, *Partition Coefficient and Bioaccumulation of Selected Organic Chemicals*, 11 ENVT'L SCI. & TECHNOLOGY 475 (1977).

21. H.R. REP. NO. 1341, 94th Cong., 2d Sess. 3 (1976).

22. National Emission Standards for Hazardous Air Pollutants, 42 U.S.C. § 1857c-7 (1970).

23. Toxic and Pretreatment Effluent Standards, 33 U.S.C. § 1317 (Supp. V 1975); Oil and Hazardous Substance Liability, 33 U.S.C. § 1321 (Supp. V 1975).

Environmental Pesticide Control Act,[24] the Safe Drinking Water Act,[25] the Occupational Safety and Health Act,[26] the Food, Drug and Cosmetic Act,[27] the Consumer Product Safety Act,[28] the Federal Hazardous Substances Act,[29] and the recent amendments to the Solid Waste Disposal Act.[30]

Reliance on these statutory provisions to control hazardous substances also is proving to be unsatisfactory. The regulatory approach generally adopted under these statutes consists of the creation of short lists of hazardous chemicals. Under the Clean Air Act, only five hazardous air pollutants (beryllium, asbestos, mercury, vinyl chloride, and benzene) have been designated.[31] The original list of toxic substances published under FWPCA contained only nine pollutants: aldrin, endrin, DDT, toxaphene, PCB's, benzidine and its salts, and all compounds containing cadmium, mercury, or cyanide.[32] Three years later, under a settlement agreement arising from a series of lawsuits brought by environmental groups, EPA agreed to expand the list to sixty-five toxic pollutants and classes of pollutants and to control them under various sections of FWPCA.[33] Among the classes are dichloroethylenes, haloethers, halomethanes, nitrophenols, polynuclear aromatic hydrocarbons, and the organic and inorganic compounds of toxic metals such as lead, mercury, and nickel.[34] The 1977 amendments to FWPCA incorporated the requirements to control these substances.[35]

Until October 1977,[36] the Occupational Safety and Health Administration (OSHA) sought to control toxic substances by the same chemical-by-

24. 7 U.S.C.A. § 136 (West Supp. 1977).
25. 42 U.S.C. § 300f (Supp. V 1975).
26. 29 U.S.C. § 651 (1970).
27. 21 U.S.C. § 321 (1970).
28. 15 U.S.C. § 2051 (Supp. V 1975).
29. 15 U.S.C. § 1261 (1970).
30. 42 U.S.C.A. § 6901 (West Supp. 1977).
31. For the rules on the first three, *see* National Emissions Standards for Hazardous Air Pollutants, 40 C.F.R. § 61 (1976). For vinyl chloride, *see* National Emission Standards for Hazardous Air Pollutants—Vinyl Chloride—Proposed Rules, 42 Fed. Reg. 28,154 (1977). For benzene, *see* National Emission Standards for Hazardous Air Pollutants: Addition of Benzene to List of Hazardous Air Pollutants, 42 Fed. Reg. 29,332 (1977). These are in addition to the ambient air standards promulgated under the Clean Air Act.
32. In the preamble to this list of nine pollutants, EPA presented a longer list of chemicals which it said may be designated in the future. Toxic Pollutant Effluent Standards, 38 Fed. Reg. 24,342-44 (1973).
33. Natural Resources Defense Council v. Train, 8 ERC 2120 (D.D.C., June 8, 1976).
34. *Id.* at 2129 (Appendix A).
35. P.L. No. 95-217 (1977).
36. On October 4, 1977, OSHA proposed a new, generic procedure for regulating carcinogens. Identification, Classification and Regulation of Toxic Substances Posing a Potential Occupational Carcinogenic Risk, 42 Fed. Reg. 54,148 (1977) (to be codified at 29 C.F.R. § 1910) [hereinafter cited as OSHA Toxic Substance Rules]. OSHA's proposal discusses the problems of the relationship between available and reliable research techniques and the control of carcinogens.

chemical approach, with the same result.[37] As the General Accounting Office reported:

> As of September 30, 1976, OSHA had established permanent standards on 15 toxic substances: vinyl chloride, asbestos, and 13 other chemicals considered to be carcinogens. Based on the past rate of progress, it will take over 100 years to establish needed standards on existing substances. Also, the estimated 500 new substances being introduced might require more standards than are being issued each year.[38]

In each case, many more chemicals could have been named than are actually listed. Only the most suspect chemicals are being regulated, while an enormous number of substances which also warrant control are being ignored.

Recognizing the inadequacies of existing testing methods, Congress opened the way to create a new and feasible regulatory scheme by authorizing regulation of chemicals by categories.

II

CONGRESSIONAL AUTHORIZATION TO USE CATEGORIES IN ADMINISTERING TSCA

This section examines the statutory provisions and supporting legislative history of TSCA which authorize EPA to regulate chemicals on the basis of categories or groups. As a preliminary matter, however, it is helpful to understand the regulatory procedures provided under TSCA, in order to see how and when EPA might use categorization to control toxic substances.

A. Statutory Scheme for Regulation

For purposes of regulation, TSCA divides chemicals into two groups: (1) currently used or "old" chemicals; and (2) "new" chemicals or significant new uses of "old" chemicals. "Old" chemicals are defined as chemicals manufactured or processed in the United States within the three-year period immediately prior to the issuance of applicable regulations by EPA.[39] The Administrator of EPA must compile and keep current the list of "old" chemicals, pursuant to section 8(b) of the Act.[40] The section 8(b) inventory provides notice to manufacturers as to which chemicals are considered "old" for purposes of regulation.[41] In regulating an "old" chemical, EPA must evaluate the potential risks posed by the chemical and, depending on

37. OSHA faces a predicament very similar to that of the EPA. As Ray Marshall, Secretary of Labor, described it when announcing the new regulations: "Trying to control carcinogenic substances on a case-by-case basis is like trying to put out the forest fire one tree at a time." N.Y. Times, Oct. 4, 1977, at 18, col. 1.

38. GENERAL ACCOUNTING OFFICE, DELAYS IN SETTING WORKPLACE STANDARDS FOR CANCER-CAUSING AND OTHER DANGEROUS SUBSTANCES 10-11 (May 10, 1977).

39. 15 U.S.C.A. § 2607(b) (West Supp. 1977).

40. *Id.* § 2607(b).

41. *Id.* § 2602(9).

the facts uncovered, consider the need for additional testing or for the establishment of regulations concerning the manufacture, use, or disposal of the chemical.[42]

TSCA establishes an interagency committee to assist EPA in establishing priorities for the testing of "old" chemicals.[43] The main task assigned to the committee is the selection and listing, in order of priority, of up to fifty chemical substances or mixtures that EPA should evaluate first. The committee must publish its recommendation in the Federal Register, together with an explanation for the committee's decision.[44] In response, EPA either must initiate a rule-making procedure or explain in the Federal Register the reasons for its inaction.[45]

Initially, "new" chemicals and significant new uses of "old" chemicals are treated differently than established uses of "old" chemicals. A manufacturer or processor either of a "new" chemical or of an "old" chemical about to be put to a significant new use must give EPA ninety days notice of its intention to manufacture or process such a chemical.[46] EPA must decide within the ninety days whether it intends to compel testing or to impose regulations. EPA may extend this period for an additional ninety days for good cause.[47] If EPA does not act, the manufacturer or processor is free to proceed, and the "new" chemical becomes an "old" one, joining the other "old" chemicals on the section 8(b) inventory.[48]

TSCA requires a determination of potential harm before EPA can require testing or regulate the manufacture, use, or disposal of a chemical. The severity of the action EPA takes depends on the degree of certainty of EPA's determination that a substance presents "an unreasonable risk of injury to health or the environment." Some actions are authorized if EPA determines that a substance "*may present* an unreasonable risk," while more restrictive actions are authorized only if EPA determines that a substance "*will present* an unreasonable risk."[49]

If a chemical satisfies the "may present" standard, EPA may undertake the following actions: (1) test the chemical, pursuant to section 4(a);[50] (2) list the chemical on a "risk list," compiled pursuant to section 5(b)(4)(i);[51] and (3) regulate the chemical temporarily pending the devel-

42. *Id.* §§ 2603(a), 2605(a).
43. *Id.* § 2603(e).
44. *Id.* § 2603(e)(1)(B).
45. *Id.* § 2603(f)(2).
46. *Id.* § 2604(a).
47. *Id.* § 2604(c).
48. *Id.* § 2607(b).
49. *Id.* §§ 2603(a), 2604(b)(4), 2604(e)-(f), 2605(a) (emphasis added).
50. *Id.* § 2603(a)(1)(A). The burden rests with the manufacturer or processor to develop data regarding the health and environmental effects of chemicals.
51. *Id.* § 2604(b)(4)(A)(i).

opment of information and testing pursuant to section 5(e).[52]

A higher degree of certainty is required before EPA may regulate a chemical on a permanent basis. Permanent regulation requires "a reasonable basis to conclude" that a chemical "presents or will present" an unreasonable risk.[53] For any chemical that fits this standard, EPA may issue rules prohibiting[54] or limiting[55] its manufacture, processing or distribution, or may require warning labels[56] or monitoring.[57]

The term "unreasonable risk" is not defined in the Act. The House Report explains that, although there were several attempts to define the term, it would be impossible, in keeping with the purpose of the Act, to do so.[58] Instead, EPA is to define "unreasonable risk" in light of the economic and social impacts of controlling the use or manufacture of the chemical.[59]

TSCA authorizes judicial review of rule-making procedures initiated under the Act.[60] A party may challenge EPA regulations both when seeking anticipatory relief and when defending against an alleged violation. The standard of review is the "substantial evidence" test.[61] TSCA also establishes various judicial procedures through which EPA can seek to enjoin the manufacture or use of certain chemicals.[62]

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52. *Id.* § 2604(e).

53. *Id.* § 2605(a).

54. *Id.* § 2605(a)(1)(A).

55. *Id.* § 2605(a)(1)(B).

56. *Id.* § 2605(a)(3).

57. *Id.* § 2605(a)(4).

58. The House Report stated:

> During the hearings a number of witnesses recommended that the bill include a definition of unreasonable risk. Because the determination of unreasonable risk involves a consideration of probability, severity, and similar factors which cannot be defined in precise terms and is not a factual determination but rather requires the exercise of judgment on the part of the person making it, the Committee did not attempt a definition of such risk. In general, a determination that a risk associated with a chemical substance or mixture is unreasonable involves balancing the probability that harm will occur and the magnitude and severity of that harm against the effect of proposed regulatory action on the availability to society of the benefits of the substance or mixture, taking into account the availability of substitutes . . . and other adverse effects which such proposed action may have on society.
>
> The balancing process described above does not require a formal benefit-cost analysis under which a monetary value is assigned to the risks associated with the substance and to the cost to society of proposed regulatory action on the availability of such benefits. Because a monetary value often cannot be assigned to a benefit or cost, such an analysis would not be very useful.

H.R. REP. NO. 1341, 94th Cong., 2d Sess. 13-14 (1976).

59. 15 U.S.C.A. § 2601(c) (West Supp. 1977).

60. *Id.* § 2618(a). Rule-making is authorized in § 2603(a) (requiring testing); § 2604(a)(2) (requiring notification of manufacture of significant new uses of chemicals); § 2604(b)(4) (compiling the "risk list" of chemicals; see text accompanying notes 43-45 *supra*); § 2605(a) (requiring regulation of chemicals); § 2605(e) (regarding control of polychlorinated biphenyls); § 2607 (regarding reporting and retention of information by manufacturers and processors).

61. *Id.* § 2618(c)(1)(B). See text accompanying notes 130-148 *infra*.

62. *Id.* §§ 2604(e)-(f), 2606. Such an injunction may issue for chemicals pending completion of testing or for chemicals imminently hazardous to humans or the environment.

B. *Statutory Provision for Regulating Chemicals by Category*

In administering the regulatory scheme outlined above, EPA may act according to categories of chemicals. TSCA provides that "[a]ny action authorized or required to be taken by [EPA] under any provision of this Act . . . may be taken . . . with respect to a category of chemical substances or mixtures."[63] The Act defines "category of chemical substances" in the broadest terms, with one potential category explicitly excluded: the category of "new chemicals."[64] A category may be based upon the chemical substances' similarity in molecular structure; in physical, chemical, or biological properties; in use; in mode of entrance into the human body or into the environment; or by any other similarity suitable for classification for the purpose of the Act. "Category of mixtures" is defined in identical terms.[65]

In addition to these general provisions, TSCA specifically authorizes the use of categories with respect to the section 8(b) inventory of "old" chemicals.[66] Also, TSCA authorizes the interagency committee charged with establishing priorities for the testing of "old" chemicals to use either individual substances or "groups of substances" in making its list.[67]

The Act specifies no separate procedures for establishment of a category. The absence of separate procedures is consistent with TSCA's authorization of the use of categories whenever suitable as part of the regular administrative procedures in testing, reporting, or regulating.[68]

In addition to the explicit statutory language contained in TSCA, further evidence of Congress' intent to use categories in controlling toxic

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63. *Id.* § 2625(c). The entire provision reads as follows:

(c) ACTION WITH RESPECT TO CATEGORIES.

(1) Any action authorized or required to be taken by the Administrator under any provision of this Act with respect to a chemical substance or mixture may be taken by the Administrator in accordance with that provision with respect to a category of chemical substances or mixtures. Whenever the Administrator takes action under a provision of this Act with respect to a category of chemical substances or mixtures, any reference in this Act to a chemical substance or mixture (insofar as it relates to such action) shall be deemed to be a reference to each chemical substance or mixture in such category.

(2) For purposes of paragraph (1):

(A) The term 'category of chemical substances' means a group of chemical substances the members of which are similar in molecular structure, in physical, chemical, or biological properties, in use, or in mode of entrance into the human body or into the environment, or the members of which are in some other way suitable for classification as such for purposes of this Act, except that such term does not mean a group of chemical substances which are grouped together solely on the basis of their being new chemical substances.

(B) The term 'category of mixtures' means a group of mixtures the members of which are similar in molecular structure, in physical, chemical, or biological properties, in use, or in the mode of entrance into the human body or into the environment, or the members of which are in some other way suitable for classification as such for purposes of this Act.

64. *Id.* § 2625(c)(2)(A).

65. *Id.* § 2625(c)(2)(B).

66. *Id.* § 2607(b)(2).

67. *Id.* § 2603(e)(1)(A).

68. *Id.* § 2625(c)(1).

substances under TSCA may be found in the Act's legislative history. From the first proposal submitted by the Council on Environmental Quality (CEQ) to the enactment of TSCA, it appeared that some use of classes or categories would play a role in administering the Act. In 1971, CEQ recommended that the Administrator, when issuing standards for testing, should issue such rules "for various classes and uses of new substances."[69] The bill introduced in the House in 1973 contained a broad authorization to take action by "class of chemical substance."[70] Although Congress did not pass this bill, the subsequent versions introduced in both the House and the Senate in 1976 contained provisions authorizing the use of categories.[71] The House and Senate provisions were similar, and the conference report adopted the House's language.[72] This version became law.[73]

References to categorization appear throughout the committee reports accompanying TSCA. The Senate Report describes the purpose of categories in broad terms: "to facilitate the efficient and effective administration of the Act."[74] As an example, the Senate Report suggests that EPA may use categories to compile the section 8(b) inventory of "old" chemicals in order that "every variation in the distribution of a polymer chain length would not be automatically subject to the pre-market notification requirement."[75] The Report cautions, however, that "categories are not to be used in the section 8(b) inventory so as to effectively provide exemptions for new chemical substances intended to be covered under the pre-market notification provisions."[76] In other words, EPA may use categories to minimize the burdens placed on industry by the pre-market notification requirement so long as the effect of such action is to facilitate, rather than to undermine, the administration of TSCA.[77]

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69. COUNCIL ON ENVIRONMENTAL QUALITY, TOXIC SUBSTANCES, at vi, 22 (1971), *reprinted in House Comm. on Interstate and Foreign Commerce, Legislative History of the Toxic Substances Control Act* 757-84 (1976).

70. H.R. 5356, 93rd Cong., 1st Sess. § 3(b) (1973).

71. S. 3149, 94th Cong., 2d Sess. § 26(c) (1976); H.R. 14032, 94th Cong., 2d Sess. § 26(c) (1976).

72. H.R. REP. NO. 1679, 94th Cong., 2d Sess. 102, *reprinted in* [1976] U.S. CODE CONG. & AD. NEWS 4539, 4587.

73. 15 U.S.C.A. § 2625(c) (West Supp. 1977).

74. S. REP. NO. 698, 94th Cong., 2d Sess. 31, *reprinted in* [1976] U.S. CODE CONG. & AD. NEWS 4491, 4521.

75. *Id.* The Conference Report expresses a similar sentiment, stating that the conferees expected that the Administrator would find categories useful in deciding what constitutes a significant new use pursuant to section 5(a)(2). H.R. REP. NO. 1679, 94th Cong., 2d Sess. 102 (1976), *reprinted in* [1976] U.S. CODE CONG. & AD. NEWS 4539, 4587.

76. *Id.*

77. The House Report also supports the use of categories to compile the section 8(b) inventory, where justified on a specific, health, and environmental basis. The underlying rationale is similar to that offered by the Senate:

> By listing a category of chemical substances, minor modifications or variations in the formulation or structure of a chemical substance which would have insignificant health or environmental consequences would not automatically be subject to the

The House Report also illustrates the various purposes categories may serve. For example, the Report suggests that under certain circumstances EPA could compel the testing of a whole category of chemicals at a time.[78] The advantage of acting according to category is that EPA, in the words of the House Report, "will not have to make the requisite finding [of harm] for such action with respect to every chemical within the category."[79] As an additional effect, one which is favorable to industry, the Report notes that testing chemicals by category may lead to exemption of a chemical from the testing requirement, thereby saving a manufacturer "unnecessary time and expense."[80]

Earlier in the Report, the House Committee indicates that it would be appropriate for EPA to evaluate the risks of an untested chemical based on its structural similarity to a chemical with known adverse or environmental effects. The House Report states the Committee's conclusion as follows:

> The finding that a substance or mixture may cause or significantly contribute to an unreasonable risk is intended by the Committee to focus the Administrator's attention on those chemical substances and mixtures about which there is a basis for concern, but about which there is inadequate information to reasonably predict or determine the effects of the substance or mixture on health or the environment. For example, if one substance is structurally similar to a second chemical with known adverse health or environmental effects, the Administrator could reasonably conclude that the first chemical may cause or significantly contribute to an unreasonable risk.[81]

This statement is consistent with the House Committee's acceptance of

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notification requirements of section 5. For instance, the Administrator could use categories so that reporting would not be required as a result of changes such as the following: polymers or co-polymers which vary only in the proportion of starting materials or catalysts used, or in molecular weight, molecular weight distribution, chain structure or crystallinity; changes within an existing chemical substance in the proportions of colorants, stabilizers, antioxidants, fillers, solvents, carriers, surfactants, plasticizers, and other adjuvants which are themselves reported as existing substances; variations in the proportion of alloyed metals in iron and steel products and other metal alloys; variations in naturally occurring substances or mixtures (such as crude oil, natural gas, minerals, or ores) and the resulting variations in extracts or refined products therefrom; variations in reported reactive mixtures whose commercial or end-use product is electric energy (batteries); and salts which result from the combination of an existing inorganic anion with an existing inorganic cation.

H.R. REP. No. 1341, 94th Cong., 2d Sess. 44 (1976).

78. 15 U.S.C.A. § 26(c) (West Supp. 1977); H.R. REP. No. 1341, 94th Cong., 2d Sess. 61 (1976). The requisite circumstances are met when EPA

> finds that the manufacture, distribution in commerce, processing, use, or disposal of a category of chemical substances may cause or significantly contribute to an unreasonable risk, that there are insufficient data and experience with respect to that category, and that testing of that category of substances is necessary to develop data.

H.R. REP., *supra*.

79. *Id.*

80. *Id.*

81. *Id.* at 17.

the view that "whenever scientifically possible, a generic [or group] approach [should be followed] for the regulation of chemicals."[82] The House Committee cites with approval the National Academy of Sciences' report, which explicitly advocates a generic approach.[83]

Support for categorization also is implicit in Congress' call for screening techniques as part of the regulatory process under TSCA. The existence of and the potential for additional screening techniques appears to have been of concern to Congress. The House Report emphasizes the need for modern screening tests to monitor and predict potential harm, concluding that tests such as the Ames Test and animal tests, though perhaps not able to provide certainty, "can provide a reasonable basis for regulatory action to protect against potential long-term adverse effects."[84] TSCA directs EPA, in coordination with the Department of Health, Education and Welfare, to undertake research "directed toward the development of rapid, reliable, and economical screening techniques for carcinogenic, mutagenic, teratogenic, and ecological effects of chemical substances and mixtures."[85]

Although Congress does not define such screening techniques, the intent is to utilize scientific techniques which avoid random and after-the-fact selection of target chemicals, and which instead allow for prediction of harm prior to its emergence in the human population.[86] Categorization performs that function, permitting a rapid sorting of chemicals by probable toxic effect, and leading to a prediction of potential injury.[87]

This conclusion, together with the statutory provisions and legislative history discussed above, indicates that EPA is authorized to use categories in administering the Act. The next section proposes a means by which EPA can categorize chemicals.

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82. *Id.* at 61.

83. The National Academy of Sciences' Committee on Principles of Decision Making For Regulating Chemicals in the Environment has recommended to EPA that:

> A matrix or generic approach, as opposed to an ad hoc procedure, should be adopted whenever scientifically possible for the regulation of chemicals. (For example, when a hazard from a particular pesticide is determined, EPA should attempt, to the extent its resources permit, to examine the other members of that pesticide class at the same time. To investigate the hazards of 2,4,5-T, for example, without examining other phenoxy herbicides is both inefficient and needlessly risky.)

NAT'L ACADEMY OF SCIENCES, DECISION MAKING FOR REGULATING CHEMICALS IN THE ENVIRONMENT 96 (1975) [hereinafter cited as REGULATING CHEMICALS].

84. H.R. REP. NO. 1341, 94th Cong., 2d Sess. 5-6 (1976).

85. 15 U.S.C.A. § 2609(c) (West Supp. 1977).

86. H.R. REP. NO. 1341, 94th Cong., 2d Sess. 5-6 (1976).

87. As noted in the Introduction, the sorting can be performed on the basis of volume, use, property, or effect. Here we shall focus on categorization according to structure-activity relationships for use in the prediction of acute toxicity, carcinogenicity, persistence, or any other activity.

III

PROPOSED BASIS FOR REGULATORY POLICY: CATEGORIZATION OF CHEMICALS ACCORDING TO STRUCTURE-ACTIVITY RELATIONSHIPS

In the absence of specific information on the toxicity of each chemical, categorization based on structure-activity relationships can fulfill the goals of TSCA. The study of structure-activity relationships seeks to find the association between a substance's physical and chemical properties and its effect on biological activity. Structure-activity relationships have been used for years in the development of new commercial products. Scientists try to predict drug[88] and pesticide[89] efficacy by starting with a compound of known structure and activity, and measuring changes in activity with variations in structure; they monitor biological activity as the functional groups of atoms attached to specific sites of a chemical are varied. In the same manner, structure-activity relationships may be applied to the study of toxic effects within a family of compounds;[90] the kinds of biological activities important in this context include such effects as acute or chronic toxicity, carcinogenicity, mutagenicity, and teratogenicity, as well as the ability to bioaccumulate, persist, or otherwise disrupt the environment.

The crucial assumption behind the structure-activity approach is that one can make reasonable inferences about a chemical's properties by grouping it in a class with other chemicals of similar structure that have known effects.[91] While significant, this assumption is no different in kind from those which have traditionally been made in applying the results of many toxicological tests. Most scientists have long accepted as a basis for sound regulatory policy the inference that, if a chemical substance causes cancer in test animals, then that chemical has a strong likelihood of causing cancer in humans.[92] While there are significant physiological differences between a

88. W. PURCELL, G. BASS, & J. CLAYTON, STRATEGY OF DRUG DESIGN, A MOLECULAR GUIDE TO BIOLOGICAL ACTIVITY (1973).

89. Neely, *The Hansch Structure-Activity Approach As An Aid in Designing New Biologically Active Chemicals*, 114 ADVANCES IN CHEMISTRY 268 (1972).

90. *See, e.g.* Szabo & Reynolds, *Structure-Activity Relationships for Ulcerogenic and Adrenocorticolytic Effects of Alkyl Nitriles, Amines, and Thiols*, 11 ENVT'L HEALTH PERSPECTIVES 135 (1975); Proceedings of a Symposium Held in Burlington, Ontario Sponsored by the Standing Committee on the Scientific Basis for Water Quality Criteria of the Joint Commission's Research Advisory Board, STRUCTURE-ACTIVITY CORRELATIONS IN STUDIES OF TOXICITY AND BIOCONCENTRATION WITH AQUATIC ORGANISMS (G. Veith & D. Konasewich, eds.) (1975); SCIENCE INFORMATION SERVICES DEP'T, FRANKLIN INSTITUTE RESEARCH LABORATORIES, STRUCTURE-ACTIVITY CORRELATION BIBLIOGRAPHY, (Environmental Protection Agency Rep. No. 560/1-75-001, 1975); P. CRAIG & J. WAITE, ANALYSIS AND TRIAL APPLICATION OF CORRELATION METHODOLOGIES FOR PREDICTING TOXICITY OF ORGANIC CHEMICALS, (Environmental Protection Agency Rep. No. 560/1-76-006, 1976) [hereinafter cited as CRAIG & WAITE].

91. See notes 88-90 *supra*.

92. Litigants have not been quick to accept the validity of the inference as a basis for regulation, however. In *Environmental Defense Fund v. EPA* (aldrin/dieldrin), 510 F.2d 1292 (D.C. Cir. 1975) and *Environmental Defense Fund v. EPA* (chlordane/heptachlor), 548 F.2d 998 (D.C. Cir. 1976), proponents of the pesticides attacked the reasonableness of EPA's position

mouse, rat, or hamster, and a human being, ethical constraints against testing carcinogens on humans dictate the need to accept the hypothesis that there is an association between animal and human carcinogens.[93]

Just as it is ethically, if not empirically, compelling to base regulatory policy on the assumption that animal carcinogens present a danger to humans, so too is it compelling to assume further that chemicals which are structurally similar will have similar effects on biological activity and thus should be treated as a class. Because of the potentially vast number of chemicals, a policy based on the assumption that each one must be dealt with individually most likely would be either too lenient, allowing the use of dangerous substances due to lack of time and resources to complete thorough testing, or too restrictive, delaying the use of beneficial chemicals for the same reasons. Reliance on structure-activity relationships is thus one method of attempting to ensure public safety without unduly hampering chemical technological progress.

At the outset, three possible approaches to categorization may be suggested. Chemicals may be grouped according to: (1) small variations in structure; (2) structural or chemical similarities; and (3) empirical structure-activity relationships. The first is the strictest and most limiting scheme; the last is the most broad. Each has its own merits and difficulties and should be analyzed separately.

A. Small Variations in Structure

Where there are only small variations in structure among chemicals, the basis for categorization is sound on both sides of the structure and activity equation. Some changes in structure are so small that it is impractical, and often difficult, to separate the compounds. In turn, little change in reactivity is anticipated among members of the class. Examples of this type

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that one may infer risk to humans based on laboratory experiments for carcinogenesis. The courts upheld EPA's principles as derived from EPA's experience and expertise.

OSHA's proposed rules on carcinogens are based on the proposition (among others) "that a toxic substance, determined as a carcinogen in a mammalian test animal system . . . is to be treated *as a policy matter* as posing a carcinogenic risk to humans." OSHA Toxic Substances Rules, *supra* note 36, at 54,148.

93. All chemicals that cause cancer in man, with the exception of arsenic, also cause cancer in at least one animal species. On the other hand, not all animal carcinogens have been shown to be human carcinogens. COUNCIL ON ENVIRONMENTAL QUALITY, ENVIRONMENTAL QUALITY, SIXTH ANNUAL REPORT 30 (1975) [hereinafter cited as CEQ REPORT]. A second possible exception is benzene. While benzene is known to cause leukemia in humans, there is no unequivocal evidence demonstrating that it is also an animal carcinogen. Occupational Exposure to Benzene, 43 Fed. Reg. 5,918, 5,932(1978).

During the recent saccharin controversy, Professor David Baltimore, a Nobel Laureate for his work in molecular biology, argued that "[a]ny implication that animal studies are not predictive of human beings leaves one in the extremely unfortunate situation of saying there's no way to know what is carcinogenic to human beings. I think the animal studies are as good as we have for predicting carcinogenesis in human beings and we have to go with them." Culliton, *Cancer Society Takes Pro-Saccharin Stand*, 196 SCIENCE 276 (1977).

of category include polymers and alloys, for which small changes in the proportion of the chemical constituents have little effect on the reactivity of the product.[94]

Polychlorinated biphenyls (PCB's) are an example of the use and acceptance of this simple type of categorization for distinct chemicals. "PCB's" is a generic term for 210 theoretically possible compounds and their isomers, all of which are recognized as having similar chemical characteristics. The variations arise from the number and location of chlorine atoms substituted on the biphenyl ring system. Rather than attempt the non-trivial task of separating out each compound according to its molecular structure, PCB's are treated as a class.[95] While there are variations in toxic potential among the members of the PCB family, it is now generally accepted that the similarities outweigh the differences in acute and chronic effects as well as in carcinogenicity and persistence in the environment.[96]

When small changes in structure involve small changes in activity, the similarities dominate, so that categorization has been a common method of grouping the compounds; indeed, it is often a necessary method of classifying them.

B. Structural or Chemical Similarities

Unlike the class of categories discussed above, there is no ambiguity about the identity, use, or production of the individual chemicals in classifications based upon structural or chemical similarities. However, there are sufficient similarities in structure to indicate similarities in physical or chemical properties.

If bromine is substituted for chlorine on the biphenyl ring system, one obtains polybrominated biphenyls (PBB's). Chlorine and bromine are members of the same family of chemical elements, the halogens; chlorine, the lighter element of the two, is directly above bromine in the Periodic Table. Thus, one may expect PCB's and PBB's to exhibit similar chemical properties. The major difference between them is physical: bromine has a larger atomic weight and radius than chlorine. Therefore, since PCB's are exceptionally hazardous, PBB's may also be expected to be toxic. Because of the 1973 PBB disaster in Michigan,[97] a full-scale testing program on PBB's was

94. Often, synthesizing one member of the class involves the production of other members of the class; in fact, one may set out to produce not only one member of the category but a mixture of some of them.

95. EPA's proposed rules for the regulation of PCB's use the following definition: "PCB chemical substances are defined as chemical substances which are limited to the biphenyl molecule that has been chorinated to various degrees." *Polychlorinated Biphenyls (PCBs)*, 42 Fed. Reg. 26,565, 26,571 (1977) (to be codified in 40 C.F.R. § 761.2(s)).

96. Ahmed, *PCB's in the Environment*, 18 ENVIRONMENT 6 (March, 1976). Since PCB's always occur as mixtures, and are characterized by their total chlorine content, there is wisdom in testing and regulating mixtures rather than individual compounds.

97. Carter, *Michigan's PBB Incident: Chemical Mix-Up Leads to Disaster*, 192 SCIENCE 240 (1976). PBB was accidently fed to cattle, and was passed through their milk to humans.

undertaken. The results are still incomplete, but preliminary research reveals harmful PBB effects in human and animals. PBB's cause neurological changes as well as immunological abnormalities. Like PCB's, they persist and bioaccumulate in the environment.[98] However, while PCB's are known to cause cancer, the evidence against PBB's is still only speculative.[99]

Although the Michigan tragedy took place in 1973, the first thorough investigation of the toxic hazards of PBB's did not begin until March 1976, when the Governor of Michigan appointed a scientific panel to "review all scientific data available on PBB,"[100] including an analysis of the "long-term health implication of exposure to PBB."[101] The panel found that "there [were] no available data since the effects of long-term chronic exposure to PBB in animals had not been studied and the human exposure was too short."[102] Thus, the panel confronted the problem of making a toxicological assessment in the absence of information. The panel's reaction is especially noteworthy:

> The Panel then followed the usual toxicological practice of looking at results of exposure to structurally related chemicals—in this case, PCB.
>
> The validity of this comparison was based on the following considerations:
>
> (1) PCB and PBB exhibit similar chemical, biochemical and toxicological characteristics with PBB generally more reactive than PCB. For example, PBB is 100 times more effective than PCB in increasing the liver's ability to metabolize drugs, i.e. in inducing the hepatic microsomal drug metabolizing system; is equal to PCB in stimulating hepatic mitochondrial respiration, is 10 times more effective in increasing the plasma cholesterol level and is 100 times more effective in decreasing protein synthesis—all in animals.
>
> (2) The symptoms seen in the human exposure to PCB in Japan were similar to those claimed for exposure of humans to PBB e.g. skin lesions, visual disturbances, neurological symptoms, fatigue, and liver function disturbances.
>
> The Panel was most impressed with the published data on the cancer effects of PCB. . . .
>
> Once the Panel became aware of the animal data on cancer

98. These findings were reported at a Workshop on Scientific Aspects of Polybrominated Biphenyls, PBB, October 24-25, 1977, at the Kellogg Center for Continuing Education, Michigan State University, East Lansing. *See also* Bekesi, Holland, Anderson, Fischbein, Rom, Wolff, & Selikoff, *Lymphocyte Function of Michigan Dairy Farmers Exposed to Polybrominated Biphenyls*, 199 SCIENCE 1207 (1978).

99. Kimbrough, Burse, Liddle, & Fries, *Toxicity of Polybrominated Biphenyl*, II LANCET 602 (1977).

100. 1977 *Toxic Substances Hearings, supra* note 18, at 33 (Statement of Dr. I.A. Bernstein, Chairman of Michigan's Scientific Advisory Panel on PBB).

101. *Id.*

102. *Id.*

> arising from exposure to PCB, it became clear that there was presumptive evidence for risk from long-term exposure to its related compound, PBB, on which no adequate experimental work had been done. In fact, the ultimate experiment in human disease—exposure of people—was actually in progress. However, the Panel was not aware at that time of the magnitude of the experiment.[103]

The panel was willing to draw inferences about the toxicity of PBB's on the basis of structure-activity relationships: the evidence that its chemical relatives, PCB's, were toxic and especially that they were carcinogenic.

A second example of a category of chemicals with similar structures and activities is the category of chlorofluorocarbons.[104] Members of this group are fully saturated hydrocarbons (*i.e.*, with no carbon-carbon double bonds). All of the carbon-hydrogen bonds have been replaced by carbon-chlorine or carbon-fluorine bonds. These compounds are generally stable in the biosphere, but scientists believe that the compounds photo-dissociate in the stratosphere, releasing chlorine, which catalyzes the destruction of the ozone layer. Thus, while there may be differences in the chemical structure of compounds in the class, there is one significant similarity in activity—they all pose a threat to the ozone layer. The category of chlorofluorocarbons is large,[105] and there are variations within the category, both in the environmental stability and in the number of chlorine atoms which might be released. (Both are factors in determining the degree and rate of ozone depletion.) Once again, however, these factors are less important than their common effect of depleting the ozone layer, which results in increasing the amount of ultraviolet radiation reaching and disrupting the biosphere.[106]

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103. *Id.* at 33-34.

104. These compounds are more precisely defined as fully halogenated chlorofluoroalkanes. *See, e.g.*, EPA's proposed rules. Toxic Substances Control: Fully Halogenated Chlorofluoroalkanes, 42 Fed. Reg. 24,542 (1977) (to be codified in 40 C.F.R. § 712.1) [hereinafter cited as EPA Rules]. *See also* the FDA proposed rules. Certain Fluorocarbons (Chlorofluorocarbons) in Food, Food Additives, Drugs, Animal Food, Animal Drugs, Cosmetics and Medical Device Products as Propellants in Self-Pressurized Containers, 42 Fed. Reg. 24,547 (1977) (to be codified in 21 C.F.R. § 2.125(a)(1)). The compounds are also known as halocarbons and fluorocarbons.

105. Regulations limiting the use of these compounds as aerosol propellants have been proposed. While many chemicals are covered under the proposed definition (see note 104 *supra*), only four of them are actually affected. Of these, two, trichlorofluoromethane (F-11) and dichlorodifluoromethane (F-12), are the most troublesome because they are produced in large quantities. The present contribution of chlorine by the two other members of the category (F-114 and F-115) is small by comparison. EPA Rules, *supra* note 104, at 24,543. Nevertheless, the regulations apply to all members of the class: "Regardless of whether or not a fully halogenated chlorofluoroalkane is being used or could be used, the restrictions are applied to all members of this class to eliminate the existing problem and to preclude any possibility of the same problem reemerging with other similar compounds." *Id.* at 24,546.

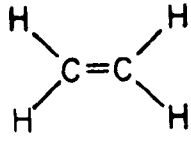
106. *See generally* NAT'L ACADEMY OF SCIENCES, HALOCARBONS: ENVIRONMENTAL EFFECTS OF CHLOROFLUOROMETHANE RELEASE (1976); NAT'L ACADEMY OF SCIENCES, HALOCARBONS: EFFECTS ON STRATOSPHERIC OZONE (1976).

Relating position on the Periodic Table to chemical or physical activity is certainly not new; indeed, this is the study of chemistry. In the same manner that scientists can draw parallels between the activities of chlorine and bromine, they can predict the environmental effects of one element based on another element's biochemical reactions. When mercury was found to be converted into the neurotoxin methyl mercury by bacteria, and through bioaccumulation in fish, inflicting its hazard on man, scientists turned their attention to the threat posed by other metals discharged into active ecosystems. Their chemistry-based inferences about biotransformations proved accurate:

> It is possible to predict which other heavy metals can be transformed in the same way as mercury. For example, by using the same approach as that used with methylmercury, one can predict that tin, palladium, platinum, gold, and thallium will be methylated in the environment, but that lead, cadmium, and zinc will not be methylated. . . . All these predictions have proved to be correct. . . . The heavy metals that are methylated should be watched closely by environmental agencies.[107]

In the heavy metals example above, scientists have begun to form an understanding of the biochemical reaction mechanisms involved. Their comprehension of the physiological mechanisms of toxicology, however, is much less developed. Often scientists do not know whether toxic activity is based on the molecule's physical or chemical properties. A molecule may interfere with the body's natural biochemical reactions because of its electron distribution (a chemical property), because of its shape (a physical property), or because of some combination of the two.

Structural similarities have been related to carcinogenicity in the family of vinyl chloride and related compounds, which are derivatives of the carbon-hydrogen compound, ethylene:



In 1971, a report of an animal inhalation study provided the first evidence that vinyl chloride is a carcinogen.[108] Since then, much more data

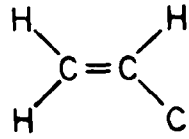
107. Wood, *Biological Cycles for Toxic Elements in the Environment*, 183 SCIENCE 1051 (1974). *See also* Ridley, Dizikes, & Wood, *Biomethylation of Toxic Elements in the Environment*, 197 SCIENCE 329 (1977).

108. Viola, Bigotti, & Caputo, *Oncogenic Response of Rat Skin, Lungs, and Bones to Vinyl Chloride*, 31 CANCER RESEARCH 516 (1971).

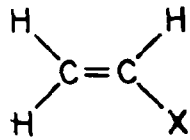
has been collected to support this conclusion.[109] Epidemiological studies have shown that occupationally exposed workers have a higher incidence of cancer—especially angiosarcoma, an otherwise rare liver tumor—than does the rest of the population.[110]

The finding that vinyl chloride is carcinogenically active suggests that compounds which are structurally related to it may also be carcinogenic. If scientists understood the process by which vinyl chloride interferes with normal cell function and division to cause cancer, they would be able to determine which aspects of its chemical structure are crucial in carcinogenesis. With this knowledge, researchers could identify the precise structural category all of whose members share vinyl chloride's carcinogenic properties. While scientists do not yet understand the cause of cancer, there are nevertheless many structural families that merit consideration.

Vinyl chloride has a structure identical to ethylene except that one of the hydrogen atoms has been replaced by a chlorine atom (Cl):



Vinyl chloride can be described in several ways, each of which suggests a category. First, it is a mono-substituted ethylene; this type of compound can be represented by the general formula:



where "X" stands for any functional group other than hydrogen. (If "X" is chlorine, the formula is a representation of vinyl chloride.) Two important members of this family are acrylonitrile, where "X" is the cyanide (C≡N) functional group:

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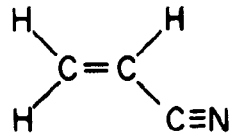
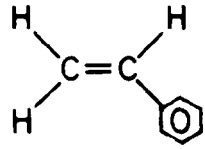
109. *See generally* ENVIRONMENTAL PROTECTION AGENCY, SCIENTIFIC AND TECHNICAL ASSESSMENT REPORT ON VINYL CHLORIDE AND POLYVINYL CHLORIDE (Environmental Protection Agency Rep. No. 600/6-75-004, 1975); STANDARD SUPPORT AND ENVIRONMENTAL IMPACT STATEMENT: EMISSION STANDARD FOR VINYL CHLORIDE (Environmental Protection Agency Rep. No. 450/2-75-009, 1975).

110. *See generally Toxicity of Vinyl Chloride—Polyvinyl Chloride*, 246 ANNALS OF THE N.Y. ACAD. OF SCIENCES (1975); INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, 7 IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN 291 (1974).



and styrene, where "X" is the phenyl functional group, (⬡):



Each is manufactured in huge quantities; in 1976, 1.52 billion pounds of acrylonitrile and 6.3 billion pounds of styrene were produced.[111] Experimental evidence now indicates that acrylonitrile is both mutagenic and carcinogenic, and styrene may be mutagenic.[112]

Thus, while there is no evidence to suggest that ethylene ("X"=H, hydrogen) is carcinogenic, the substitution of one hydrogen leads to the formation of at least three definite or suspected mutagens or carcinogens. The extent to which the members of the category of mono-substituted

111. Anderson, *Top 50 Chemicals Regain Output Lost in 1975*, CHEMICAL & ENGINEERING NEWS 32, 37 (May 2, 1977).

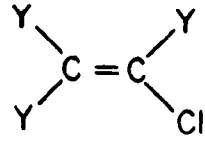
112. J. Quast, R. Enriquez, C. Wade, C. Humiston, & B. Schwetz, *Toxicity of Drinking Water Containing Acrylonitrile (AN) in Rats: Results After 12 Months* (March 1977), *cited in* Dep't of Labor, Occupational Safety and Health Administration, Occupational Exposure to Acrylonitrile, 42 Fed. Reg. 33,043 (1977) (to be codified in 29 C.F.R. § 1910); Bronson, *Chemical Acrylonitrile Linked to Cancer in Workers Exposed to It, Agency Says*, Wall St. J., June 30, 1977, at 6, col. 2; Milvy & Wolff, *Mutagenic Studies with Acrylonitrile*, 48 MUTATION RESEARCH 271 (1977). The question of styrene's carcinogenicity turns on whether and how it is metabolized by humans; many metabolites, including the epoxide (or oxide), have been shown to be mutagenic. Milvy & Garro, *Mutagenic Activity of Styrene Oxide (1, 2 Epoxyethylbenzene) A Presumed Styrene Metabolite*, 40 MUTATION RESEARCH 15 (1976); Stoltz & Withey, *Mutagenicity Testing of Styrene and Styrene Epoxide in "Salmonella typhimurium,"* 17 BULL. ENVT'L CONTAMINATION & TOXICOLOGY 739 (1977). As of November, 1977, both acrylonitrile and stryrene epoxide were being tested by the National Cancer Institute (NCI). TECHNICAL INFORMATION RESOURCES BRANCH, NCI, CHEMICALS BEING TESTED FOR CARCINOGENICITY BY THE BIOASSAY PROGRAM (Nov. 1, 1977) (printout).

Mutagenicity strongly suggests carcinogenicity. See discussion of the Ames test at text accompanying note 19 *supra*. The Commissioner of the Food and Drug Administration, in his decision holding that the acrylonitrile plastic beverage containers were unsafe, affirmed that positive Ames tests "are highly important in indicating the need for further investigation into the carcinogenic potential of acrylonitrile." Food & Drug Adm., U.S. Dep't Health, Education & Welfare, Indirect Additives—Polymers: Acrylonitrile Copolymers Used to Fabricate Beverage Containers—Final Decision, 42 Fed. Reg. 48,538 (1977). The Commissioner found that while a positive Ames test is insufficient as proof of carcinogenicity, it is sufficient to require complete animal testing of a chemical.

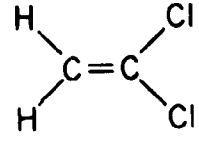
It should be noted, however, that the Ames hypothesis has not gained complete acceptance. *See, e.g.*, Sivak, *supra* note 19.

ethylenes are carcinogenic is unknown since many of the compounds in the class have not been tested for activity, but this is a category to consider.

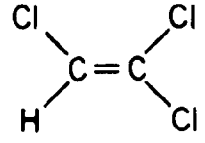
Vinyl chloride is also a member of the category of unsaturated chlorinated ethylenes, compounds of the form:



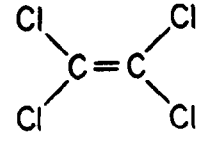
where each "Y" is either a chlorine or a hydrogen atom. The category consists of six compounds: three compounds with two chlorine atoms, and three compounds which have either one, three, or four chlorine atoms. There is a strong suggestion that vinylidene chloride:



is carcinogenic.[113] In 1976, the National Cancer Institute (NCI) reported that trichloroethylene:



is carcinogenic in mice.[114] Then in 1977, NCI disclosed that tetrachloroethylene:

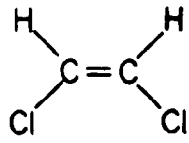


113. Cesare Maltoni has shown that vinylidene chloride causes kidney cancer in certain strains of mice. Wall St. J., Feb. 23, 1977, at 18, col. 2. Dow Chemical's studies on rats showed no traces of cancer. *Vinylidene Chloride: No Trace at Dow*, CHEMICAL & ENGINEERING NEWS 21 (Mar. 14, 1977). Vinylidene chloride, upon activation, was positive on the Ames test. Bartsch, Malaveille, Montesano, & Tomatis, *Tissue-Mediated Mutagenicity of Vinylidene Chloride and 2-Chlorobutadiene in "Salmonella typhimium,"* 255 NATURE 641 (1975) [hereinafter cited as Bartsch, *et al.*].

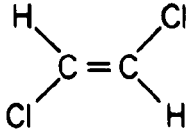
114. NATIONAL CANCER INSTITUTE, CARCINOGENESIS BIOASSAY OF TRICHLOROETHYLENE (Dep't Health, Education & Welfare No. (Nat'l Inst. of Health) 76-802, 1976).

showed carcinogenic activity.[115] The remaining two members of the category, the 1,2-dichloroethylenes (the cis- and trans- isomers):

(Cis)



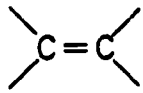
(Trans)



have shown no activity.[116] In this case, however, at least half of the category is carcinogenic.

Other potential categorization schemes for vinyl chloride analogs include substituting chlorine with other members of the halogen family, especially bromine, or substituting a variety of functional groups for more than one hydrogen atom. The possibilities are numerous. Of course, the greater the degree of substitution, and the larger the number of possible functional groups which may be used, the bigger the resulting category.

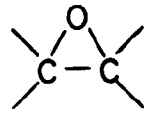
The appropriate category can be defined more accurately, of course, when the mechanism of carcinogenesis is known. With vinyl chloride, one current hypothesis is that the mammalian organism converts the carbon-carbon double bond:



115. Laboratory tests showed that tetrachloroethylene, also known as perchloroethylene, is a liver carcinogen in male and female mice. NATIONAL CANCER INSTITUTE, BIOASSAY OF TETRACHLOROETHYLENE FOR POSSIBLE CARCINOGENICITY (Dep't Health, Education & Welfare No. (Nat'l Inst. of Health) 77-813, 1977).

116. Greim, Bonse, Radwan, Reichert, & Henschler, *Mutagenicity in Vitro and Potential Carcinogenicity of Chlorinated Ethylenes as a Function of Metabolic Oxirane Formation*, 24 BIOCHEMICAL PHARMACOLOGY 2013 (1975) [hereinafter cited as Greim, *et al.*].This study also showed no mutagenicity for tetrachloroethylene.

into the corresponding epoxide:



which purportedly is the ultimate carcinogenic agent.[117] If this hypothesis proves to be correct, it will greatly facilitate the selection of the category most in need of attention.[118]

C. *Empirical Structure-Activity Relationships*

In the vinyl family of compounds discussed in the last category, the similarities in structure are observable. Yet it is still not clear which property of the chemicals is responsible for their carcinogenicity. As we noted, the active chemical carcinogen may not be the observable chemical structure but rather some intermediate reaction product, such as an epoxide. When sufficient information is known, potentially toxic chemicals can be classed according to an observable, or latent, active fragment; that is, according to the functional group responsible for the biologic activity.

In other cases, the common thread between members of an active class may be even less obvious. Interference with the normal physiological processes may be structural (that is, physical), but the activity might not necessarily arise from a specific, recognizable configuration of atoms; rather it may result from any of a set of similar shape and charge distributions. Therefore, in developing a category, one might select candidates according to the presence of atoms with similar size and shape, rather than the presence of a specific observable structure.

Developments in computer analysis of chemicals have simplified the task of identifying such "non-apparent" chemical families. Computer programs are now available which classify compounds according to their active or potentially active chemical fragments. Thus, in the same manner that compounds are assigned names on the basis of their structure, they can also be typed by their structural components through the use of a computer.[119]

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117. Bonse, Urban, Reichart, & Henschler, *Chemical Reactivity, Metabolic Oxirane Formation and Biological Reactivity of Chlorinated Ethylenes in the Isolated Perfused Rat Liver Preparation*, 24 BIOCHEMICAL PHARMACOLOGY 1829 (1975); Bartsch,*et al., supra* note 113; Greim *et al., supra* note 116. *See generally* Miller & Miller, *The Metabolism of Chemical Carcinogens to Reactive Electrophiles and Their Possible Mechanisms of Action in Carcinogenesis*, in CHEMICAL CARCINOGENS (1976) (American Chemical Society Monograph 173).

118. Categorization, and the logic upon which it is based, is a dynamic, evolutionary process, changing to conform with new data as they are discovered. A National Academy of Sciences' panel on testing potentially hazardous chemicals has pointed out that: "As more information on new structures becomes available, the old guidelines must often be discarded. For instance, it was once assumed that to be carcinogenic, an aromatic amine needed at least two aromatic rings. Now, more thorough tests of simpler aromatic amines have shown that such a premise does not hold." NAT'L ACADEMY OF SCIENCES, PRINCIPLES FOR EVALUATING CHEMICALS IN THE ENVIRONMENT 143 (1975) [hereinafter cited as EVALUATING CHEMICALS].

119. FEIN-MARQUART ASSOC., INC., HANDBOOK OF CIDS (CHEMICAL INFORMATION AND DATA SYSTEM), CHEMICAL SEARCH KEYS (1973).

With the use of sub-structure search systems, compounds with the same structural fragments can be separated into categories.[120] The system is extraordinarily flexible and provides a nearly unlimited number of ways to categorize compounds.

The power of this technique was demonstrated in a recent study in which the acute toxicity[121] of organic compounds could be predicted with substantial reliability on the basis of the presence of certain key structural groups. The study concluded:

> The results obtained to date from this study support the validity of the basic assumption, namely; that structural fragments can be assigned incremental toxicity values which may serve to estimate the resulting toxicity of the entire molecule. This result was by no means a foregone conclusion, especially when the complex nature of lethality and the problem of poor duplicability of [toxicity] results are considered.[122]

Thus, the potential for predicting the nature of toxic actions without knowing the exact physiological mechanism is available through such statistical and computer-generated empirical findings. This third type of categorization is the least well developed, but over the long term, as theories of toxicity evolve, empirical structure-activity relationships will play an increasingly important role in predicting potential hazard.

The selection of one approach over another should be a matter of policy. The greater the possibility of human and environmental exposure to structural analogs of a known toxic chemical and the greater the potential harm they may cause, the more broadly the category should be defined. The same balancing process that is required to determine what is a reasonable or unreasonable risk is required to draw boundaries around chemical families in the absence of complete information.[123]

D. Scientific Acceptance of Categorization

Categorization, as a regulatory approach, is gaining acceptance within the scientific community. The most compelling endorsement was recently given by the National Academy of Sciences' study group on the regulation of toxic substances, which noted:

> Another step that would help in setting rational priorities is to use a matrix or generic approach so that when one problem comes to

120. Heller, Milne, & Feldmann, *A Computer-Based Chemical Information System*, 195 SCIENCE 253 (1977); J. MILLER, CSS (CHEMICAL SUBSTRUCTURE SEARCH SYSTEM), USER'S MANUAL, ON-LINE RETRIEVAL SUBSYSTEM (1976) (prepared for the Environmental Protection Agency by Fein-Marquart Associates, Inc., Baltimore, Maryland).

121. Acute toxicity was measured by the compound's LD_{50}, which is the interpolated lethal dose of a chemical necessary to kill half (50 percent) of a population of experimental animals.

122. CRAIG & WAITE, *supra* note 90, at 2-31.

123. *See Judging Safety*, in W. LOWRANCE, OF ACCEPTABLE RISK, SCIENCE AND THE DETERMINATION OF SAFETY 75 (1976).

> the Agency's attention, other closely related problems are also reviewed for possible action. For example, when a hazard from a particular pesticide is determined, EPA should attempt, to the extent its resources permit, to examine the other members of that pesticide class at the same time. To investigate the hazards of PCB's without examining polybrominated biphenyls is both inefficient and needlessly risky.
>
> EPA should adopt, whenever scientifically possible, a generic approach, as opposed to an ad hoc procedure, for the regulation of chemicals.[124]

The need to set priorities in evaluating risks was given added emphasis by another Academy panel, whose members wrote:

> Because of the tens of thousands of natural and synthetic substances present in the environment, it becomes necessary to establish a reasonable system of priorities for the further study of those substances not yet fully evaluated. To study every chemical to the same extent would represent an unjustifiable expenditure of effort that did not contribute significantly to protection of public health. It is neither practicable nor necessary to undertake experimental toxicological studies of every chemical to which man is exposed: to do so would be to assign equal importance to problems of unequal risk. This would deny the value of experience in assessing probable risk. . . .
>
> The first step in this dilemma therefore, should be the preparation of guidelines for classifying chemicals into categories, such as (1) recognized as probably safe because of adequate and valid use experience, (2) of low priority of concern because the use level is at such an insignificant or trivial level, and (3) critical.[125]

While the panelists expressed caution about placing total reliance on structure-activity relationships,[126] they concluded:

> Many important decisions, at least about the sequence of testing, can be made without testing at all on the basis of analogies with other known chemicals. Structure-activity relations are reasonably well

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124. REGULATING CHEMICALS, *supra* note 83, at 33. This reference to the potential hazards of PBB's was published in 1975, before the full extent of the Michigan PBB poisoning was recognized.

125. EVALUATING CHEMICALS, *supra* note 118, at 111-12.

126. The Academy panel's cautionary language, which might be taken too broadly, reads as follows:

> The chemical structure of the material and its similarity to known chemical carcinogens should be taken into account. Structure-activity correlations and a knowledge of what functional groups are associated with carcinogenicity of the molecule can furnish some leads concerning suspect compounds. However, total reliance on structure-activity relationships as an index of carcinogenic risk is a hazardous venture. If the only reason for testing a material of little environmental importance is that its structure is closely akin to that of a known carcinogen, it is not necessary to give it high priority for testing.

Id. at 143. The emphasis of this cautionary language is on the wastefulness of full-scale testing of chemicals "of little environmental importance" as much as on a rigid application of structure-activity correlations.

> understood for some groups of chemicals and some toxic effects, less well known for others. However, many new industrial chemicals differ only trivially from other known materials and relatively few fall into genuinely unknown groups. Those that do will require correspondingly more complex testing.[127]

Categorization based on small variations in structure (the first approach) has won wide approval. Categorization based on structural or chemical similarities (the second approach), though less favored, is gaining support, and is on the threshold of receiving official endorsement as a valid scientific principle both because of increased understanding of the underlying chemical and structural processes responsible for adverse effects, and because of the undeniable need for more efficient methods for determination of hazard.

Categorization is not intended to be a definitive determination of toxicity in itself.[128] It is a tool to aid in that determination. Therefore, the question of certainty of hazard within a category is not relevant, since categorization is but the first step in the evaluation of hazard. No matter how one categorizes compounds, relationships like those in the vinyl family point to probabilities of hazard which are greater than the probabilities based on random predictions, *i.e.*, the average probability that any chemical selected from among all chemicals is toxic.

As CEQ pointed out:

> If the chemical structure of a chemical resembles that of a compound known to be carcinogenic, there is a likelihood that both are carcinogenic. However, the converse is not necessarily true; the fact that a chemical is not similar in structure to any known carcinogen does not prove that it is safe. . . .
>
> Most carcinogenic compounds known today fall into a few categories of chemical structure. Theoretically it is possible to predict that other chemicals falling into these categories will also be carcinogenic; unfortunately, we simply do not known enough to predict with confidence that a compound will not be carcinogenic if it falls outside these structural categories. Testing, therefore, is necessary to confirm the noncarcinogenicity of a compound.[129]

CEQ's language is particularly noteworthy: testing of those compounds related to known carcinogens must confirm *non*carcinogenicity. Thus, the effect of this language would be to shift the burden of proof, on the basis of structure-activity relationships, from safe until proven carcinogenic to carcinogenic until proven safe.

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127. *Id.* at 21.

128. Indeed, there are many pairs of chemicals which are structurally related but which show different biological activity; these are sometimes used to evaluate the reliability of screening tests. See, *e.g.*, Purchase *et al.*, *Evaluation of Six Short Term Tests for Detecting Organic Chemical Carcinogens and Recommendations for Their Use*, 264 NATURE 624 (1976).

129. CEQ REPORT, *supra* note 93, at 32-33.

IV

CATEGORIZATION AND THE "SUBSTANTIAL EVIDENCE" TEST

Assuming EPA can develop categories of suspect chemicals, the question remains whether the scientific hypothesis underlying a category constitutes "substantial evidence" to support a decision to test or regulate a chemical. Without this showing, the specific regulatory action may not withstand judicial scrutiny.[130]

Under the substantial evidence test, courts review an agency's findings to determine if they are supported by substantial evidence on the record considered as a whole. In recent environmental cases, however, several courts have broadened the traditional notion of what constitutes evidence for purposes of the test. The leading case is *Industrial Union Dep't, AFL-CIO v. Hodgson*,[131] where the petitioner challenged action under the Occupational Safety and Health Act of 1970.[132] In *Industrial Union Dep't*, the court held that:

> [T]here are areas where explicit factual findings are not possible, and the act of decision is essentially a prediction based upon pure legislative judgment, as when a Congressman decides to vote for or against a particular bill.
>
> . . . .
>
> [P]olicy choices of this sort are not susceptible to the same type of verification or refutation by reference to the record as are some factual questions. Consequently, the court's approach must necessarily be different . . . [from the usual application of the substantial evidence test].[133]

In concluding its discussion of the appropriate standard of review, the court stated that:

> What we are entitled to at all events is a careful identification by the Secretary [of Labor], when his proposed standards are challenged, of the reasons why he chooses to follow one course rather than another. Where that choice purports to be based on the existence of certain determinable facts, the Secretary must, in form as well as substance, find those facts from evidence in the record. By the same token, when the Secretary is obliged to make policy judgments where no factual certainties exist or where facts alone do not provide the answer, he should so state and go on to identify the considerations he found persuasive.[134]

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130. 15 U.S.C.A. § 2618(c) (West Supp. 1977).

131. 499 F.2d 467 (D.C. Cir. 1974).

132. The House Report cites *Industrial Union Dep't* with approval, indicating its support for the court's novel application of the substantial evidence test. H.R. REP. NO. 1341, 94th Cong., 2d Sess. 55-56 (1976).

133. 499 F.2d at 474-75.

134. *Id.* at 475-76.

Thus, in the area of predicting health risks, the court held that, when evaluating the sufficiency of evidence supporting an administrative decision, it could accord as much weight to policy judgments based on predictions of harm as traditionally is reserved for factual findings. Although this application of the substantial evidence test is limited to certain cases, the requisite circumstances are met when the questions involved "are on the frontier of scientific knowledge, and consequently as to them insufficient data [are] presently available to make a fully informed factual determination."[135] Thus, the rationale is that the "[d]ecision-making must in that circumstance depend to a greater extent upon policy judgments and less upon purely factual analysis."[136]

The District of Columbia Circuit Court of Appeals, sitting *en banc*, applied the *Industrial Union Dep't* standard of review in its decision in *Ethyl Corp. v. EPA*.[137] This case, decided under the Clean Air Act, came down three months prior to the enactment of TSCA. The court discussed at length the precautionary nature of regulatory action designed to protect health and the environment, and expressly held that hypothetical and other forms of scientific evidence not reaching the level of certainty were relevant to a judgment of risk posed by chemicals.[138] In *Ethyl*, the Administrator had relied in part upon the hypothesis, consistent with known evidence, that urban children are likely to ingest lead from gasoline combustion that has fallen to the ground and mixed with dust. The hypothesis admittedly was not proven as fact, and was offered only in support of the evidence already presented. However, the dustfall hypothesis had particular importance because it established a link between lead emissions from automobile exhaust and growing children, a significant group highly vulnerable to lead poisoning. The court found that the precautionary nature of the "will endanger" standard of the Clean Air Act encompassed a wide range of permissible proof, including a supportable and reasonable hypothesis: "It is therefore no objection to the dustfall hypothesis that it is merely a hypothesis. A supportable and reasonable hypothesis may well form the basis for regulations under Section 211(c)(1)(A)" of the Clean Air Act.[139]

As Judge Skelly Wright wrote:

> Sometimes, of course, relatively certain proof of danger or harm from such modifications [of our environment] can be readily found. But, more commonly, "reasonable medical concerns" and theory long precede certainty. Yet the statutes—and common

135. *Id.* at 474.
136. *Id.*
137. 541 F.2d 1, 8 ERC 1785 (D.C. Cir.) (*en banc*), *cert. denied*, 426 U.S. 941, 8 ERC 2200 (1976).
138. *Id.* at 28, 8 ERC at 1812.
139. *Id.* at 44, 8 ERC at 1817.

> sense—demand regulatory action to prevent harm, even if the regulator is less than certain that harm is otherwise inevitable.[140]

Judge Wright limited the use of hypothesis evidence to cases where the decision is one in which the decision-maker is charged with a precautionary duty to protect public health and where the hypothesis is consistent with known facts and information. TSCA, of course, meets the first standard. The second test can be met by the strength of the hypothesis establishing the category and the surrounding factual evidence.

The second appellate opinion in *Reserve Mining Co. v. EPA,*[141] involving asbestiform discharges into Lake Superior, also accepts the use of hypothetical evidence to predict risk.[142] In *Reserve Mining*, as Judge Wright later characterized it in *Ethyl*, the evidence "constituted no more than . . . a hypothesis."[143] The issue turned on whether the district court could rely on a hypothesis that *ingestion* of asbestos endangered health based upon epidemiological studies that associated *inhalation* of asbestos with cancer. The court approved the finding of danger, stating that:

> These concepts of potential harm, whether they be assessed as "probabilities and consequences" or "risk and harm," necessarily must apply in a determination of whether any relief should be given in cases of this kind in which proof with certainty is impossible. The district court, although not following a precise probabilities-consequences analysis, did consider the medical and scientific evidence bearing on both the probability of harm and the consequences should the hypothesis advanced by the plaintiffs prove to be valid.
>
> In assessing probabilities in this case, it cannot be said that the probability of harm is more likely than not. Moreover, the level of probability does not readily convert into a prediction of consequences. On this record it cannot be forecast that the rates of cancer will increase from drinking Lake Superior water or breathing Silver Bay air. The best that can be said is that the existence of this asbestos contaminant in air and water gives rise to a reasonable medical concern for the public health. The public's exposure to asbestos fibers in air and water creates some health risk. Such a contaminant should be removed.[144]

Congressional approval of the scope of review set forth in these decisions is seen in the House Report accompanying TSCA. Language consistent with the approach in *Industrial Union Dep't* and *Ethyl* appears in the Report:

> When, as here, regulatory action is intended to be taken to prevent the occurrence of harm . . . such action often must be based not only [on] consideration of facts but also on consideration of scien-

140. *Id.* at 25, 8 ERC at 1801.
141. 514 F.2d 492 (8th Cir. 1975) (*en banc*).
142. *Id.* at 519-20.
143. Ethyl Corp. v. EPA, 541 F.2d at 46, 8 ERC at 1817.
144. Reserve Mining Co. v. EPA, 514 F.2d at 520.

> tific theories, projections of trends from currently available data, modeling using reasonable assumptions, and extrapolations from limited data.[145]

The Report cites *Industrial Union Dep't* to support the proposition that the "courts have adequately adapted to [the substantial evidence test]," explaining that the Committee intended "that the reviewing court engage in a searching review of the Administrator's reasons and explanations for the Administrator's conclusions."[146] Thus, the legislative history extends the precedential value of these decisions beyond their local jurisdictions to all courts hearing cases brought under TSCA.[147] There is nothing inherent in the "substantial evidence" test which precludes reliance upon categorization and, hence, its materiality would depend upon the underlying scientific persuasiveness in much the same manner that other extrapolations and inferences from data support an estimate of risk.[148]

V

USE OF CATEGORIES TO FACILITATE THE ADMINISTRATION OF TSCA

How does categorization facilitate the control of toxic substances under TSCA? First and foremost, the use of categories eliminates a binary approach to chemical regulation. Under a categorization approach, chemicals no longer are judged either safe or unsafe. Rather, a probability of their potential harm can be estimated within a spectrum ranging from safe to unsafe. This probability estimate can then be included with the other parameters, such as affected population and degree of exposure, in the determination of "unreasonable risk" in the risk-benefit analysis required under the Act. In the analysis of vinyl chloride analogs, for instance, we suggested several different structure-activity categorization schemes, each based upon a different family of potential carcinogens. Given present knowledge, researchers can assign different subjective probabilities to the likelihood that an untested analog, a member of one of the several possible categorical families, causes cancer or is otherwise toxic. Such probability

145. H.R. REP. NO. 1341, 94th Cong., 2d Sess. 32 (1976).

146. *Id.* at 55-56.

147. 15 U.S.C.A. § 2618 (West Supp. 1977).

148. The language of TSCA elsewhere supports this understanding of the substantial evidence test. In the section on judicial review, TSCA defines "evidence" as used in "substantial evidence" to be "any matter in the rulemaking record." 15 U.S.C.A. § 2618(c)(1)(B) (West Supp. 1977). This provision, coupled with the explicit authorization to use categorization with respect to "any action authorized or required to be taken by the Administrator under any provision of this Chapter," *id.* § 2625, indicates that information derived from categories appropriately may be considered as evidence underlying the Administrator's decision.

It should be noted that the "substantial evidence" standard applies only to Administrator action under § 2503(a) (testing requirements); § 2604(b)(4) (maintenance of "risk" list); § 2605(a) (regulation of hazardous chemicals); and § 2605(e) (regulation of PCB's). *Id.* § 2618(c)(1)(B)(i). It would not apply to the use of categories by the ITC (see text accompanying notes 154-163 *infra*) or for data collection (see text accompanying notes 164-170 *infra*).

estimates allow the regulator to set priorities and to establish strategies for the prevention of harm. Thus, categorization of chemicals can be used in establishing testing priorities, regulating chemicals pending the completion of testing, gathering of data, designing data systems, and anticipating future regulatory action.

As discussed above, TSCA differentiates between the showing of harm needed for the testing of chemicals and the showing necessary for their regulation. The difference between the standards was intentional. As the House Report states in discussing the distinction with respect to testing:

> [T]he bill does not require the Administrator to find that a substance or mixture does cause or significantly contribute to or will cause or significantly contribute to an unreasonable risk. Such a finding requirement would defeat the purpose of the [testing] section, for if the Administrator is able to make such a determination, regulatory action to protect against the risk, not additional testing, is called for.[149]

The Conference Report is even more explicit: testing requirements are to be based upon a finding that a chemical "may present an unreasonable risk."[149a] This requires only a basis for concern, not definite knowledge. The Report, addressing the testing requirement based upon the "may present" standard, states that:

> [T]he conferees intend to focus the Administrator's attention on those chemical substances and mixtures about which there is a basis of concern, but about which there is inadequate information to reasonably predict or determine their effects on health or the environment. The Administrator need not show that the substance or mixture does or will present a risk.[150]

The inclusion of a chemical in a category of suspected toxic substances should raise sufficient "concern" over its safety to indicate that the substance "may present" an unreasonable risk, and therefore, categorization may aid in the establishment of testing priorities.

Regulation requires a higher standard of certainty. The Administrator must find that a chemical "does or will present" an unreasonable risk of injury before he can issue rules to regulate the manufacture and processing of the chemical.[151] This standard requires a greater degree of certainty and, hence, the scientific theories and facts underlying the proposed relationship must be correspondingly more certain. However, absolute certainty is not required. EPA need only find that a "reasonable basis" exists to believe that

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149. H.R. REP. No. 1341, 94th Cong., 2d Sess. 17-18 (1976).

149a. H.R. REP. No. 1679, 94th Cong., 2d Sess. 60, *reprinted in* [1976] U.S. CODE CONG. & AD. NEWS 4539, 4545.

150. *Id.* at 61, *reprinted in* [1976] U.S. CODE CONG. & AD. NEWS at 4546.

151. 15 U.S.C.A. § 2605(a) (West Supp. 1977).

a chemical will present an unreasonable risk.[152] As EPA gains more experience with the use of categorization of chemical substances and mixtures, it is likely that particularly strong relationships among chemical substances will support decisions to regulate them as a class.[153]

Categorization also plays a role in the drafting of recommendations by the Interagency Testing Committee (ITC),[154] the committee charged with

152. *Id.* The House Report described such basis as:

> Thus, the bill requires a reasonable basis to conclude that a substance or mixture causes or significantly contributes to or will cause, or significantly contribute to an unreasonable risk to health or environment. Such a judgment may be based upon items such as toxicological, physiological, epidemiological, biochemical, or statistical research or studies or extrapolations therefrom. A finding by the Administrator that there is such a reasonable basis must include adequate reasons and explanations for the Administrator's conclusion. It does not, however, require the factual certainty of a "finding of fact" of the sort associated with adjudication.

H.R. REP. NO. 1341, 94th Cong., 2d Sess. 32 (1976).

153. OSHA, in its proposed cancer policy, has taken a similar view. OSHA Toxic Substances Rules, *supra* note 36, at 54,168. OSHA stated that it did not intend, for the time being, to base *regulation* solely on structure-activity relationships, but it did acknowledge the applicability of structure-activity relationships to setting testing priorities. *Id.* In support of its decision to defer the use of structure-activity relationships, OSHA quoted from a 1970 National Cancer Institute (NCI) report (although the date of the report was omitted in OSHA's citation):

> The carcinogenic activity of materials can only be detected by long-term biological tests. At the present time the chemical structure or physio-chemical properties of a compound do not provide a reliable basis for prediction of freedom from carcinogenic activity. Several structure-activity correlations are valuable indicators of the possible carcinogenicity of a compound, but none can be used to classify the compound as non-carcinogenic. Short-term bioassays that determine the effects of certain chemicals on selected biologic targets have not been reliable for prediction of carcinogenic activity.

NATIONAL CANCER INSTITUTE, AD HOC COMMITTEE ON THE EVALUATION OF LOW LEVELS OF ENVIRONMENTAL CHEMICAL CARCINOGENS, REPORT TO THE SURGEON GENERAL: EVALUATION OF ENVIRONMENTAL CARCINOGENS 5-6 (1970), *reprinted in Hearings on S. 232, S. 272, S. 660, and S. 745 Before the Subcomm. on Agricultural Research and General Legislation of the Senate Comm. on Agriculture and Forestry*, 92d Cong., 1st Sess. 677 (1971).

No one would argue that structure-activity relationships provide unambiguous indicators of carcinogenicity, but since the time the NCI report was issued in April, 1970, considerable progress has been made.

The significance of OSHA's proposed policy on the use of structure-activity relationships may not be too large. OSHA itself recognized the possibility that OSHA, which has no specific authority to compel animal testing, should defer to the EPA on this issue, in view of EPA's testing authority under TSCA. OSHA has requested comments on this issue. OSHA Toxic Substance Rules, *supra* note 36, at 54,168.

154. 15 U.S.C.A. § 2603(e) (West Supp. 1977). There was some concern that an ambiguity in TSCA might prevent the ITC from recommending categories of substances. TSCA authorizes the "Administrator" to use categories. The ITC is not the Administrator and therefore it might be asserted that the ITC lacks the authority to list substances by category despite the fact that the Administrator could compel testing by category. The ITC concluded that such an interpretation is inconsistent with other provisions contained in TSCA. Initial Report of the TSCA Interagency Testing Commission to the Administrator, Environmental Protection Agency, 42 Fed. Reg. 55,027, 55,035 (1977) [hereinafter cited as Initial Report]. Its authority to advise the Administrator as to which chemicals to test and in what order should be equivalent to the Administrator's authority to compel testing. The ITC also supported its position by referring to the phrase "groups of substances or mixtures" used in the statute to describe the contents of the list prepared by the committee. However, this reference is ambiguous; it is unclear whether the term refers to grouping of priorities or substances. 15 U.S.C.A. § 2603(e) (West Supp. 1977).

submitting to EPA a list of no more than fifty chemicals for testing priority. In its first recommendation to EPA, the ITC included six categories of substances among its initial ten recommendations.[155] The ITC relied in part on structure-activity relationships in selecting from the list of 100,000 chemical substances and mixtures.[156]

The six categories selected by the ITC range from those in which the chemicals are very similar to ones in which the members are related only by the presence of a potentially toxic functional group. In fact, categories were selected from each of the three types of categories described in section III. Examples of the type 1 category (small variations in structure) include

155. Initial Report, *supra* note 154, at 55,032. The six categories are:

(1) alkyl epoxides, a category consisting of all noncyclic aliphatic hydrocarbons with one or more epoxy functional groups, *id.* at 55,051;

(2) alkyl phthalates, a category consisting of all high production (*e.g.*, 10 million lbs/year or greater) alkyl esters of 1, 2-benzene dicarboxylic acid (orthophthalic acid), *id.* at 55,052;

(3) chlorinated benzenes, both monosubstituted and disubstituted, a category consisting of four closely related chemical substances: monochlorobenzene, and ortho-, para-, and metadichlorobenzene, *id.* at 55,053;

(4) chlorinated paraffins, a category consisting of a series of mixtures of chlorination products of materials known commercially as paraffin oils or paraffin waxes, *id.* at 55,054;

(5) cresols, a category consisting of the three isomers of methyl phenol, *id.* at 55,056;

(6) xylenes, a category consisting of the three isomers of dimethyl benzene, *id.* at 55,060.

The four individual chemicals are chloromethane, hexachlor-1, 3, butadiene, nitrobenzene, and toluene. *Id.* at 55,051-060. With the possible exception of the use of categories under FWPCA, see text accompanying notes 32-34 *supra*, the use of categories by the ITC is the most dramatic example to date. It is not the first, however. In its initial decision on the use of acrylonitrile in plastic beverage bottles, the FDA Commissioner noted the relevance of structural similarity in judging a chemical's potential for carcinogenicity where there is an absence of data from direct chronic feeding studies. Food Additives: Acrylonitrile Copolymers Intended for Use in Contact with Food, 41 Fed. Reg. 23,940, 23,944 (1976). In another Federal Register notice, the FDA requested the submission of data, information, and views on the safety and use of chlorine or compounds containing chlorine in food processing. Permitted Use of Chlorine in Food Processing: Invitation to Submit Data, Information and Views, 41 Fed. Reg. 27,856 (1976). NIOSH has, in a similar fashion, solicited information for the development of criteria documents and the establishment of occupational standards for vinyls. The category includes the related chemicals vinyl acetate, vinyl bromide, vinyl chloride, vinyl fluoride, vinylidene chloride, vinylidene fluoride, and 1, 2-dichloroethylene. Request for Information: Vinyls, 42 Fed. Reg. 35,227 (1977). NIOSH had already published criteria documents for many of the vinyl analogs discussed in text accompanying notes 108-118 *supra*, including trichloroethylene, acrylonitrile, and vinyl chloride. On November 4, 1977, NIOSH went even further, asking for information on 21 classes of chemicals, including aliphatic imines, nitroalkanes, nitronaphthalenes, inorganic chlorine gases, and compounds of elements such as selenium, copper, and lithium. The Institute intends to prepare criteria documents and to recommend standards for these classes by 1982. Request for Comments on Certain Chemical/Physical Agents and Industrial Processes, 42 Fed. Reg. 57,747 (1977). Finally, TSCA directs EPA to regulate polychlorinated biphenyls as a class. 15 U.S.C.A. § 2605(e) (West Supp. 1977).

156. Initial Report, *supra* note 154, at 55,036. At a workshop in June 1977, sponsored by the Conservation Foundation and funded by EPA, the conferees noted (with one dissent) that "[t]he use of categories, at least for rules requiring testing of chemicals, is ***absolutely necessary*** if TOSCA is to live up to its promise." CONSERVATION FOUNDATION, SETTING PRIORITIES FOR CHEMICALS UNDER THE TOXIC SUBSTANCES CONTROL ACT 13 (August 1977) (Under Environmental Protection Agency Grant #7T900629010) (emphasis added).

chlorinated paraffins, which are characterized in a fashion similar to PCB's,[157] and the members of the cresol and xylene families, which in each case differ only in their spatial configurations of the functional groups.[158] Examples of type 2 categories (chemical or structural similarities) include the chlorinated benzenes, which resemble chlorinated ethylenes,[159] and the category of alkyl phthalates (any of the possible esters of the organic acid, orthophthalic acid),[160] which is akin to the example of any mono-substituted ethylene compound.[161]

The broadest category identified by the ITC, the alkyl epoxides, includes all compounds which contain one or more epoxy functional group.[162] This approaches the type 3 category. The epoxy site is believed to be carcinogenic or mutagenic.[163]

Categorization can be used by the EPA in executing the TSCA mandate to "design, establish and coordinate an efficient and effective system for the retrieval of toxicological and other scientific data which could be useful to the Administrator in carrying out the purposes of this Act. . . ."[164] Categorization facilitates the collection of relevant data, which is a necessary first step in the establishment of a retrieval system. It is important to remember that structure-activity relationships are only one of many possible categorization schemes. Categories based on type of use and scale of

157. See text accompanying notes 95-96 *supra*.

158. The definition of the three xylenes as one category is not new. When OSHA published its criteria document for xylene it noted: "Regardless of the source of raw materials from which produced, 'xylene' . . . refers to any one of or combination of the isomers of xylene: ortho-, meta-, or para-dimethylbenzene." NAT'L INSTITUTE FOR OCCUPATIONAL SAFETY & HEALTH, U.S. DEP'T HEALTH, EDUCATION & WELFARE, CRITERIA DOCUMENT: RECOMMENDATIONS FOR AN OCCUPATIONAL EXPOSURE STANDARD FOR XYLENE 1 (1975). The chemical industry does not seem eager to embrace the use of categories under TSCA. For example, a representative of Dow Chemical responded to the ITC recommendations by noting that in the case of xylenes, "[I]t might make more sense to test one xylene isomer first before testing the other two." *First Chemicals Picked for Testing Under TSCA*, CHEMICAL & ENGINEERING NEWS 14 (Oct. 25, 1977).

159. See text accompanying note 113 *supra*.

160. Also known as 1, 2-benzene dicarboxylic acid.

161. See text accompanying note 111 *supra*.

162. The only limitation on the category is that any member compound must not contain a ring structure.

163. In its preliminary list, the ITC cited other, potentially large classes categorized only by an active functional group (*e.g.*, asymmetric ketones and alkyl amines). The Committee also considered some broad categories based on uses (*e.g.*, fire retardants and fluorescent brightening agents). TOXIC SUBSTANCES CONTROL ACT INTERAGENCY TESTING COMMITTEE, PRELIMINARY LIST OF CHEMICAL SUBSTANCES FOR FURTHER EVALUATION (July, 1977). As this Article goes to press, the ITC's contractor, Clement Associates, has recommended 19 new categories as candidates for the testing list. Of particular importance is the fact that the categories were identified with the use of sub-structure search, using the TSCA Candidate List as the data base, in the manner suggested in section IV of this Article. [1978] CHEM. REG. REP. (BNA) 1594. See text accompanying notes 119-120 *supra*.

164. 15 U.S.C.A. § 2609(c) (West Supp. 1977).

production can play a major role in determining data collection, as well as testing, priorities.[164a]

By looking at the category in which a chemical appears, EPA can readily identify the toxic property about which it should gather data.[165] This shorthand method of identification permits EPA to narrow an otherwise broad search for data on a given chemical, and thus minimizes the chance of collecting irrelevant information. For example, if a chemical appears in a category of substances suspected of causing cancer at low dosages, EPA need only request information under section 8(a) which would prove or disprove the specific hypothesis relating to carcinogenicity. Information which might prove useful to an inquiry concerning the acute toxicity of a chemical might not be relevant here. In this sense, categorization allows EPA to tailor its data gathering efforts to specific needs, and in so doing, permits EPA to set priorities as to the type of information it should collect on a given chemical.[166] The result is a more efficient method of collecting information, in terms of both time and effort.

Besides providing a means, categorization also supplies the incentive to create an information network. In a subtle manner, categorization may induce EPA to develop such a network by underscoring the need to place all information in a time-saving computer system which has the capability of sorting chemicals according to potentially active fragments.[167] Because the study of empirical associations depends for its vitality on the ready availability of such structural and toxicological information, which only a computer can provide, categorization emphasizes the important role a centralized, computerized network of information plays in regulating toxic substances.[168]

164a. Structure-activity relationships are only one example of the possible use of categorization. In its latest draft strategy document, EPA suggests: "EPA might specify that manufacturers must report certain use information, for example, for all chlorinated hydrocarbons manufactured in quantities over 100,000 pounds." [1978] CHEM. REG. REP. (BNA) 1662.

165. Current proposals indicate that EPA will adopt a multi-tier system for its testing requirements. Structure-activity relationships are perfectly suited as triggering mechanisms to switch a chemical from one testing program to another, more comprehensive one.

166. Once categorization prescribes which information must be submitted to the agency, such information can become the basis for the design of reporting forms to be filled out by manufacturers and processors.

167. Under such a system, a researcher could identify, at the push of a button, the size of any category, the quantity in which each member-chemical is produced, and the purpose or purposes for which each is used. In short, by aggregating this information, a computer program could yield information about the class as a whole.

168. *See, e.g.*, note 163 *supra*. As we have repeatedly stressed, much needs to be learned about toxicity and structure-activity relationships. In this regard, any computer system should be designed with the maximum flexibility because the fragment responsible for toxicity may not yet be known. For example, today's programs work with two-dimensional representations of chemicals; it may be discovered that three-dimensional ones are needed. The computerized system that is developed should be designed to serve as a laboratory for the research and development of categorization as a technique of detecting harm, in much the same way as scientists use a laboratory to conduct experiments in the search for new tests to uncover potentially toxic substances.

Beyond emphasizing the need to develop computer programs,[169] categorization reinforces the importance of data gathering and dissemination *per se*. Presently, EPA suffers from a lack of information. As Warren Muir, the chairman of the ITC, emphasized in his letter accompanying the Committee's report: "The Committee has been hampered in its deliberations by the lack of a readily available and consolidated source of data on the many chemicals to which man and the environment are exposed."[170] Over time, as data on structure, production, and use become available, toxicologists and epidemiologists will be better able to evolve and test theories and hypotheses on modes of toxic action.

Categorization can be helpful in giving industry the notice it needs to plan economically and effectively. TSCA should be "an early warning system to signal potential dangers before products are widely dispersed and irretrievable societal danger has been unleashed."[171] The statutory scheme of TSCA in part is based upon the understanding that "the most effective and efficient time to prevent unreasonable risks to public health or the environment is prior to manufacture. It is at this point that costs of regulation in terms of human suffering, jobs lost, wasted capital expenditures, and other costs are lowest."[172] One way to regulate so as to provide manufacturers with notice and thereby avoid these consequences is through intermediate actions, somewhere between declaring a chemical safe or toxic. The "risk list" authorized by section 5(b)(4)[173] and the priority testing list to be established by the ITC are such intermediate actions. A crucial intermediate action by EPA will be the listing of the "new" uses of "old" chemicals which will be considered "significant new uses." Once such uses are defined, industry is on notice that, before a manufacturer submits a section 5 notice signifying the intent to market such a chemical, the chemical substance or mixture involved will require substantial testing. These intermediate actions are areas where categorization is useful. By warning industry of the chemical categories which bear the heaviest burden of proof of safety, industry will have a basis for assessing the probability of success of its own plans. In this sense, categorization can stabilize the regulatory climate.

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169. It is interesting to note that the need for computer programs was recognized over a decade ago. The first finding and recommendation of the *President's Science Advisory Committee, Report on Handling of Toxicological Information* (1966), was "that there exists an urgent need for a much more coordinated and more complete computer-based file of toxicological information than any currently available and further, that access to this file must be more generally available to all those legitimately needing such information." *Id.* at 10.

170. Initial Report, *supra* note 154, at 55,026. The letter further states: "Other activities under TSCA, *e.g.*, development of coordinated data systems, inventory reporting, and other information collection under Section 8, should be of considerable value in future Committee efforts." *Id.*

171. S. REP. No. 698, 94th Cong., 2d Sess. 4 (1976).

172. *Id.* at 5.

173. 15 U.S.C.A. § 2604(b)(4) (West Supp. 1977).

CONCLUSION

By granting to EPA the authority to act by categories of chemical substances and mixtures, Congress has provided a more effective means of regulating toxic substances than the traditional chemical-by-chemical approach. This Article has attempted to explain the significance of categorization based on structure-activity relationships as a regulatory scheme. Regulation of chemicals under TSCA will be difficult. Unless EPA initiates action based upon categories of chemicals, and therefore probabilities of hazard, the system of regulation may be a futile scheme for prevention of injury.