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STRATEGIES TO DETERMINE NEEDS AND PRIORITIES FOR TOXICITY TESTING

VOLUME 1: DESIGN

STEERING COMMITTEE ON IDENTIFICATION OF TOXIC AND POTENTIALLY TOXIC CHEMICALS FOR CONSIDERATION BY THE NATIONAL TOXICOLOGY PROGRAM

BOARD ON TOXICOLOGY AND ENVIRONMENTAL HEALTH HAZARDS

ASSEMBLY OF LIFE SCIENCES

NATIONAL RESEARCH COUNCIL

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EXECUTIVE SUMMARY

The National Toxicology Program (NTP) asked the National Academy of Sciences-National Research Council to address two major subjects: (1) the magnitude of compounds in the U.S. environment that require additional toxicity data with which to ascertain risks or hazards to human health, and (2) the development of valid and uniformly applicable criteria that the NTP could use to set priorities among chemicals that would be candidates for toxicity testing to determine their potential adverse public-health impact.

A study, called "Identification of Toxic and Potentially Toxic Chemicals for Consideration by the National Toxicology Program," was undertaken by three committees (now called the Committees on Sampling Strategies, on Toxicity Data Elements, and on Priority Mechanisms) that received guidance, direction, and coordination from a Steering Committee. The results of the design phase of the study are reported herein.

"SELECT UNIVERSE" OF SUBSTANCES

To define toxicity-testing needs for substances in the human environment, it was necessary to define the substances to which humans are exposed in the United States. The "select universe" was used to describe the substances to be included in this definition. Its construction relied on the search for existing lists of substances preselected for human exposure potential and computerized for reasonably easy access. A search for such lists revealed several that could be assembled to form the "select universe," provided that most duplicates could be eliminated. The lists obtained included the Toxic Substances Control Act (TSCA) Inventory, representing 48,523 chemical substances in commerce; a list of pesticides (active and inert ingredients) registered for use by the Environmental Protection Agency (EPA); a list of food additives including those approved for use by the Food and Drug Administration (FDA); a list of drugs (prescription and over-the-counter) and their formulation excipients approved for use by the FDA; and a cosmetic ingredients list of the Cosmetic, Toiletry and Fragrance Association. The result was the formation of the core of the "select universe" of substances that would be the reference for the study. It was recognized that this "select universe" had a major limitation: it did not systematically include substances that were environmental decomposition products, manufacturing contaminants, or natural substances (e.g., natural constituents of foods). To accommodate this deficiency, a miscellaneous category was considered; however, the Steering Committee elected not to include this category, because a suitable list could not be identified. The sum of the above, 63,910 substances without those from the drug list,[a] was taken as the "select universe" of substances for purposes of this study.

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[a] The list of drugs (prescription, over-the-counter, and formulation excipients) had not been received from the FDA at the time of completion of this report.

TOXICITY-TESTING NEEDS

In preparation for the evaluation of needed testing of chemicals in the human environment, general concepts and procedures were developed to serve as guides in the evaluation of data on the toxicity of chemicals in humans and surrogate species and data on known or anticipated exposure to these substances. The approach uses two sequential stages, each of which contains general operating principles and some specific elements of experimental design and data interpretation, which are supplemented with professional judgment to deal with aspects of data analysis that cannot be codified.

The first stage describes the battery of toxicity data elements (e.g., acute-oral, subchronic-inhalation, or oral-carcinogenesis) that should be available for judging the relative risk of a substance under conditions of its intended use, of its manufacture, and of its environmental dissemination and modification. The report identifies 33 types of toxicity data and several categories of chemical information from which various batteries of tests would be selected for each substance.

The second stage addresses the evaluation of the quality of individual studies to determine the extent to which their results might be suitable for predicting risks to human health from exposures to a substance. The report relies on current designs for toxicity studies and epidemiologic investigations to serve as references for later evaluations of data.

SAMPLING STRATEGIES

A method was devised to draw a sample from the "select universe" of chemicals that are of interest to the NTP. A sampling procedure is needed because determination of the toxicity-testing needs for more than 70,000 chemicals of interest to the NTP, if derived from an assessment of each of these chemicals, would far exceed current resource limitations.

An approximation to the chemical universe of interest to the NTP--the "select universe"--was used as the sampling frame for which a sampling procedure was developed. Five major categories--pesticides, cosmetics, drugs, food additives, and chemicals in commerce--were considered to encompass most of the chemicals to which humans are exposed.

A maximal final sample size of 100 chemicals was considered to be the limit of resource capability in determining the adequacy of toxicity testing and the testing needs for the "select universe." It was concluded that a double-sample, stratified, random sampling procedure was most appropriate to the sampling frame and the intended uses of the sample. These three characteristics were the guidelines in the development of the sampling method.

The lists of chemicals were kept intact in five strata of the sampling frame, from each of which a portion of the sample was drawn to permit some minimal analysis of the characteristics of each list. First, chemicals were drawn from the "select universe" to form the

initial sample. Then, a screening process was applied to a random subset of these chemicals to identify 100 chemicals that would make up the final sample. Random ordering of the initial sample before its screening was designed to eliminate order effects within the lists representing the five categories.

The sampling procedure was applied to the "select universe" after duplicate chemicals were removed to the extent practical. Chemicals for the initial sample of 700 were taken from all areas in all lists (chemicals will be added to the initial sample from the drug list when the list is received from the FDA). The part of the initial sample apportioned to each of the five categories took account of the relative sizes of the categories in the larger "select universe" from which the sample was drawn, as well as the relative degrees of interest and the relative likelihood of finding minimal toxicity information. The final sample of 100 chemicals was designed to contain 15 pesticides, 15 cosmetic ingredients, 15 drugs, 15 food additives, and 40 chemicals in commerce (10 produced at 1,000,000 lb/yr or more, 10 at less than 1,000,000 lb/yr, and 20 at rates that were unknown or inaccessible because of manufacturers' claims of confidentiality).

Eighty-five of the 100 chemicals in the sample have been selected (15 chemicals from the drug list will be added later). A range of 21 - 42% of the pesticides, cosmetics, and food additives and a range of 11 - 33% of the chemicals in commerce in the initial sample that were passed through the screening process for minimal toxicity information met minimal standards. This may reflect the proportions of chemicals with minimal toxicity information in the same categories in the much larger "select universe."

APPROACHES TO PRIORITY-SETTING

Systems for categorizing substances in terms of relative toxicity or potential public-health impact have been reviewed, with particular reference to the priority-setting needs of the NTP in ranking chemicals for toxicity testing. Study of the available schemes has helped to identify issues and problems that must be addressed and resolved in the process of designing a maximally effective system for use by the NTP. The following characteristics will be used in designing a maximally effective priority-setting system for consideration by the NTP:

- The testing strategy should permit gathering of the necessary information in a cost-effective manner, with decisions on the collection of information at each stage in the process based on the value of the information.

- A cost-effective balance should be achieved between the resources devoted to the priority-setting process and the testing itself.

- The extent to which lack of information on chemicals is a constraint on their selection and ranking for testing should be recognized.

- The system should contain a mechanism for self-evaluation and for modification to improve performance.

- The role of expert judgment should be clearly described.

- Attention should be given to the advantages of a multistage strategy that might include both screening and sorting in the selection and ranking of substances for testing.

- The system should recognize and take into account the characteristics of toxicity tests, such as rates of false-negative and false-positive results.

- The system should strive for a proper balance of resources between development and interpretation of exposure and toxicity information and the sequence in which these are most effectively acquired and used.

- Without being excessive in resource use, exposure assessment should reflect the complexity of real-life exposure situations.

- The system should ensure cost-effective and scientifically sound treatment of the uncertainties in exposure estimates and toxicity estimates.

- The toxicity evaluation process should give adequate consideration to the various types of health effects that different substances might be expected to elicit.

- The system should strive to achieve an effective balance in its use of various sources of toxicity information, such as structure-activity relationships, short-term tests, and literature review; and it should include a mechanism based on predictive data to verify conclusions.

- The system should include strategies for dealing with additive, synergistic, or antagonistic toxicologic interactions that may result from exposure to combinations of substances.

I

INTRODUCTION

BACKGROUND

Human life has always entailed exposure of humans to chemicals. The very substances we eat, drink, and breathe are composed of chemical compounds. The twentieth century has seen substantial growth in the synthesis of new molecules, some of which have proved useful to humankind in treating disease, preserving food, and reducing the cost of commodities. In recent decades, there has been widespread concern that synthetic chemical substances--growing in number and concentrations--may have some negative impact on human health. The estimates of such substances in the environment ranged as high as "hundreds of thousands" (NAS, 1975).

If one supplements the catalog of man-made materials with the naturally generated chemicals, such as those which constitute food, the list of substances to which humans are exposed may appear endless. Responding to the Toxic Substances Control Act (TSCA), the Environmental Protection Agency (EPA) has cataloged more than 55,000 substances that are now being manufactured or imported and that enter into various phases of chemical manufacture and formulation in the United States (U.S. Environmental Protection Agency, 1979). Human exposure to these agents is known only in small measure and must be characterized by inference. The TSCA Inventory excludes classes of agents that are regulated under other statutes. In contrast, food additives, pharmaceuticals (prescription and over-the-counter), and cosmetics are substances to which humans are exposed, but many are regulated under the Food, Drug, and Cosmetic Act, rather than under TSCA.

The specter of a public-health impact leads to a need for information with which to construct a credible response. Such information generally takes the form of results of toxicologic studies in laboratory animals thought to be useful for predicting human effects. The development of a strategy for obtaining appropriate information requires an understanding of the availability of toxicity data applicable to the assessment of human risk and knowledge of the number of compounds on which necessary experimental data are not yet available. The magnitude of needed testing would influence the allocation of resources needed for such research. If the testing requirements go beyond existing resources, a strategy that makes it possible to address the compounds of greatest concern is essential.

THE NATIONAL TOXICOLOGY PROGRAM

On November 15, 1978, the Secretary of the Department of Health, Education, and Welfare (DHEW), Joseph Califano, announced the establishment of the National Toxicology Program (NTP) in the DHEW, which later became the Department of Health and Human Services (DHHS) (U.S. Public Health Service, 1979). The broad goal of the

NTP is to coordinate the DHHS's activities in the testing of chemicals of public-health concern and in the development and validation of new and better-integrated test methods. Specific goals of the NTP are to extend the toxicologic characterization of chemicals being tested, to increase the rate of chemical testing (within the limits of available resources), and to develop and begin to validate a series of protocols appropriate for regulatory needs. In general, it develops scientific information about toxic and potentially toxic and hazardous chemicals--information that can be used for the prevention of chemically induced disease and for otherwise protecting the health of the American people. It provides some of the toxicologic information needed by research and regulatory agencies.

The NTP Executive Committee provides linkage between DHHS research agencies and federal regulatory agencies to ensure that the toxicology research, testing, and test development under the aegis of the NTP are responsive to the needs of those agencies and to the wants of the public. This unique and important aspect of the NTP brings together for the first time the regulatory agencies and the research agencies that are doing fundamental biomedical research.

For further information, the reader is referred to the NTP Annual Plans for fiscal years 1979, 1980, and 1981.

Because resources for developing sound scientific bases for identifying risks and hazards are limited, there is a strong impetus to select, for immediate attention, the most far-reaching chemical problems for research. It is essential to establish priorities among chemical and physical agents and to select those known or expected to have the greatest impact on human health.

It has been recognized that the methods currently used by federal agencies for assigning priorities are strikingly diverse. It is now possible and timely to review existing ranking systems and to synthesize a priority-setting framework that acknowledges and is responsive to various priority needs. Such a framework should take into account not only such basic elements as populations exposed, toxicity, and controllability, but also less-quantifiable sociologic and psychologic factors and capabilities, resources, and legislative mandates.

PURPOSE OF THE STUDY

Broadly defined, the purpose of the study is twofold: to characterize the status of toxicity information on compounds to which there is known or anticipated human exposure; and to develop and validate criteria--uniformly applicable and wide-ranging--by which to set priorities for research on substances with potential adverse public-health impact. The charge was necessarily structured into components that are described below.

ORGANIZATION OF THE STUDY AND OVERALL OBJECTIVES

A preliminary evaluation of the objectives of the study by the Board on Toxicology and Environmental Health Hazards (BOTEHH) led to the formulation of the initial strategy for the study and later to the formation of the Steering Committee to oversee the functions of three committees--the Committee on Statistical Sampling Methods (now referred to as the Committee on Sampling Strategies), the Committee on Characterization of the Status of Toxicity Data Elements for a Select Universe of Compounds (Committee on Toxicity Data Elements), and the Committee on Research of Agents Potentially Hazardous to Human Health (Committee on Priority Mechanisms).

To address the first objective, the Committees on Sampling Strategies and on Toxicity Data Elements were formed. The Committee on Sampling Strategies, composed mainly of experts in statistics, was to be responsible for evaluating sampling methods, for selecting the most appropriate sampling approach for this study, for generating a sample, and for assisting in the interpretation of results of evaluation of the sample. The Committee on Toxicity Data Elements, composed mostly of experts in the toxicologic sciences, was to be responsible for the derivation of criteria by which the sample of chemicals would be characterized with respect to toxicity data, for application of the criteria to the sample, and for interpretation of the results in relation to the sampling frame.

The Committee on Priority Mechanisms was established to formulate an approach to the setting of priorities for testing chemicals. Starting with an evaluation of existing approaches to analyze their capabilities and limitations, the Committee was to structure a detailed framework commensurate with the broad scope of the NTP and establish the framework's practicality by appropriate validation exercises. Because of the diverse elements generally considered in setting priorities, widely varied expertise in the biologic, chemical, and social sciences and in law and economics was incorporated into the Committee.

CHEMICALS OF CONCERN TO THE NTP: THE "SELECT UNIVERSE"

It is estimated on the basis of the Chemical Abstracts Service (CAS) that the known universe of chemicals consists of over 5 million entities. Many of these substances are of laboratory interest only. The substances to which humans are exposed repeatedly at work and at home would constitute a "select universe" of compounds that would conform generally to the scope of the NTP terms of reference.

In defining the "select universe" of compounds for NTP needs, two approaches were possible. First, one theoretically could use the CAS list and select substances to which extensive human exposure is known or likely. This approach was not practical--although the CAS list is computerized, it does not provide an index of exposure, and manual evaluation of such a large number of substances was beyond the physical resources of the study. Second, one could search for existing lists of substances preselected for human exposure potential and computerized for reasonably easy access. A search for such lists revealed several that could be assembled to form the "select universe," provided that most duplicates could be eliminated. The lists selected included the TSCA Inventory, representing 48,523 chemical substances in commerce;

a list of pesticides (active and inert ingredients) registered for use by the EPA; a list of food additives approved for use by the Food and Drug Administration (FDA); a list of drugs (prescription and over-the-counter) and their formulation excipients approved for use by the FDA; and a cosmetic ingredient list of the Cosmetic, Toiletry and Fragrance Association. The result was the formation of the core of the "select universe" of substances that would be the reference for the study. It was recognized that this "select universe" had a major limitation: it did not systematically include substances that were environmental decomposition products, manufacturing contaminants, or natural substances (e.g., natural constituents of foods). To accommodate this deficiency, a miscellaneous category was considered; however, the Steering Committee elected not to include this category, because a suitable list could not be identified. The sum of the above, 63,910 substances without those from the drug list, was taken as the "select universe" of substances for purposes of this study.

OBJECTIVES OF THIS REPORT

The size of the "select universe" precludes retrieving and evaluating existing toxicity data on all its constitutents to determine the extent to which additional data are needed. To approach an understanding of the status of toxicity information on the "select universe," a scheme was envisioned that would use carefully conceived sampling techniques. A probability sample could be extracted from the "select universe" and later analyzed to learn the extent and quality of toxicity data on substances in the sample. The Committee on Sampling Strategies was responsible for evaluating sampling techniques and selecting appropriate ones. The results of the Committee's work are described in Chapter II. The primary objective of creating the sample is to permit characterization of the status of toxicity information on chemicals in the sample, categorization of the quantitative distribution of toxicity data in the sample, and estimation of the proportions of chemicals in the "select universe" on which there are various degrees of toxicity data. This knowledge will be used to estimate the types and amounts of toxicity testing required to meet various goals.

To estimate the percentage of chemicals that may be of interest to the NTP, each substance in the sample must be the subject of an exhaustive search of literature on toxicity in humans and in experimental models that are believed to be qualitatively or quantitatively predictive of human responses. The information sought should include the entire toxicity data base.

The Committee on Toxicity Data Elements is responsible for the critical evaluation of the available toxicity data on the substances in the sample. It has generated two sets of criteria (see Chapter III). The first set is to be used to judge the merits of individual studies (i.e., adequacy of design and conduct of experimentation). The second set is to serve as a basis on which the minimal data-base requirements for various levels of risk evaluation (i.e., types of experimental data necessary to draw reliable conclusions) could be judged. These criteria

are the results of a specific exercise to generate and summarize general principles by which to gauge toxicity studies and data bases. These principles will be operational guides during the examination of the sample (to be reported in Volumes 2 and 3, 1982 and 1983) and will be subject to refinement based on experience and insight gained in preparing the data summaries and evaluations.

It is certain that the number of substances requiring many types of toxicologic investigation will be large and beyond the resources of the NTP for simultaneous testing. The NTP responds to nominations from participating federal agencies for the testing of agents of primary interest to these agencies. Thus, it is faced with a need for scientifically defensible ways of setting priorities among the relatively few nominations from agencies and the relatively large number of candidate substances anticipated from the "select universe." To address this issue, the Committee on Priority Mechanisms is undertaking an analysis to develop means by which the NTP can estimate the re ative degree of public-health consideration of all data on chemicals that have been examined. The results of these analyses are described in Chapter IV.

OBJECTIVES FOR LATER STAGES OF THE STUDY

This volume, the first of a planned series of three, presents results of the initial stages in evaluating testing needs for the NTP and provides means for setting priorities among chemicals for testing. It describes the terms of reference, departure points, and rationale for later evaluations. The criteria identified here may be altered as the study progresses and as new data are obtained. Consequently, the reader is advised to refer to later volumes as they become available.

Volume 2 will provide an in-depth analysis of the toxicity tests and test types on substances in the sample and will describe a priority-setting approach tailored to NTP needs.

Volume 3 is expected to contain an analysis of the sample as reflecting the composition of the "select universe," thereby indicating the magnitude of the testing task before the NTP. Concomitantly, the Committee on Priority Mechanisms will provide a priority-setting method that is comprehensive and has been demonstrated to be applicable to circumstances facing the NTP.

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II

STRATEGY FOR SELECTING A SAMPLE FROM THE "SELECT UNIVERSE"

Among the overall goals of this study are two that require assessment of the extent and adequacy of toxicity data on chemicals in the "select universe":

- To estimate the proportions of compounds in the "select universe" on which there are qualitative and quantitative toxicity data of particular statuses.
- To estimate the proportions of compounds in the "select universe" that have adequate toxicity testing and that should be considered by the NTP for additional toxicity testing and to determine the nature of that testing.

Direct assessment of these proportions for 63,910 chemicals currently present[a] in the "select universe" would exceed the resources available to the NTP for its efforts to identify chemicals with potential health hazard and determine the degree of that hazard. The committees taking part in this study faced similar resource limitations. Therefore, the decision was made in the study's planning stages to draw a small representative sample of chemicals from the "select universe." This would reduce to a manageable size the amount of data collection and assessment needed for the two goals. This sampling scheme could also be used by the NTP in its future endeavors to characterize components of its "select universe."

A major role of the Committee on Statistical Sampling Methods (commonly called the Committee on Sampling Strategies) was to develop a sampling procedure that would yield statistically valid estimates of the "select universe." That the estimates be statistically valid is especially critical because the success of the study requires, in part, that the sample be used to estimate the status of other chemicals in the "select universe" of interest to NTP. The validity of the estimates is ensured by using probability sampling, applying specified sampling rates to five categories of chemicals in the "select universe," whose sizes vary greatly: pesticides, cosmetic ingredients, drugs, food additives, and chemicals in commerce. Together, these categories embody a large collection of chemicals that form the sampling frame from which the sample is drawn. An overview of the detailed sampling process is described in Figure II-1.

THE UNIVERSE AND THE SAMPLING FRAME

The universe of known chemicals consists of over 5 million identified entities with unique molecular structures. The chemicals in the portion of this universe of interest to NTP are those which present a potential hazard to human health. Accordingly, the Committee defined a "select universe," compiled by combining lists of chemicals that were, by definition, substances to which humans are potentially exposed. These lists represented the five categories mentioned.

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[a] At the time of completion of this report, the drug list had not been received from the FDA. The number of chemicals indicated as being present in the "select universe" does not include any from the drug list.

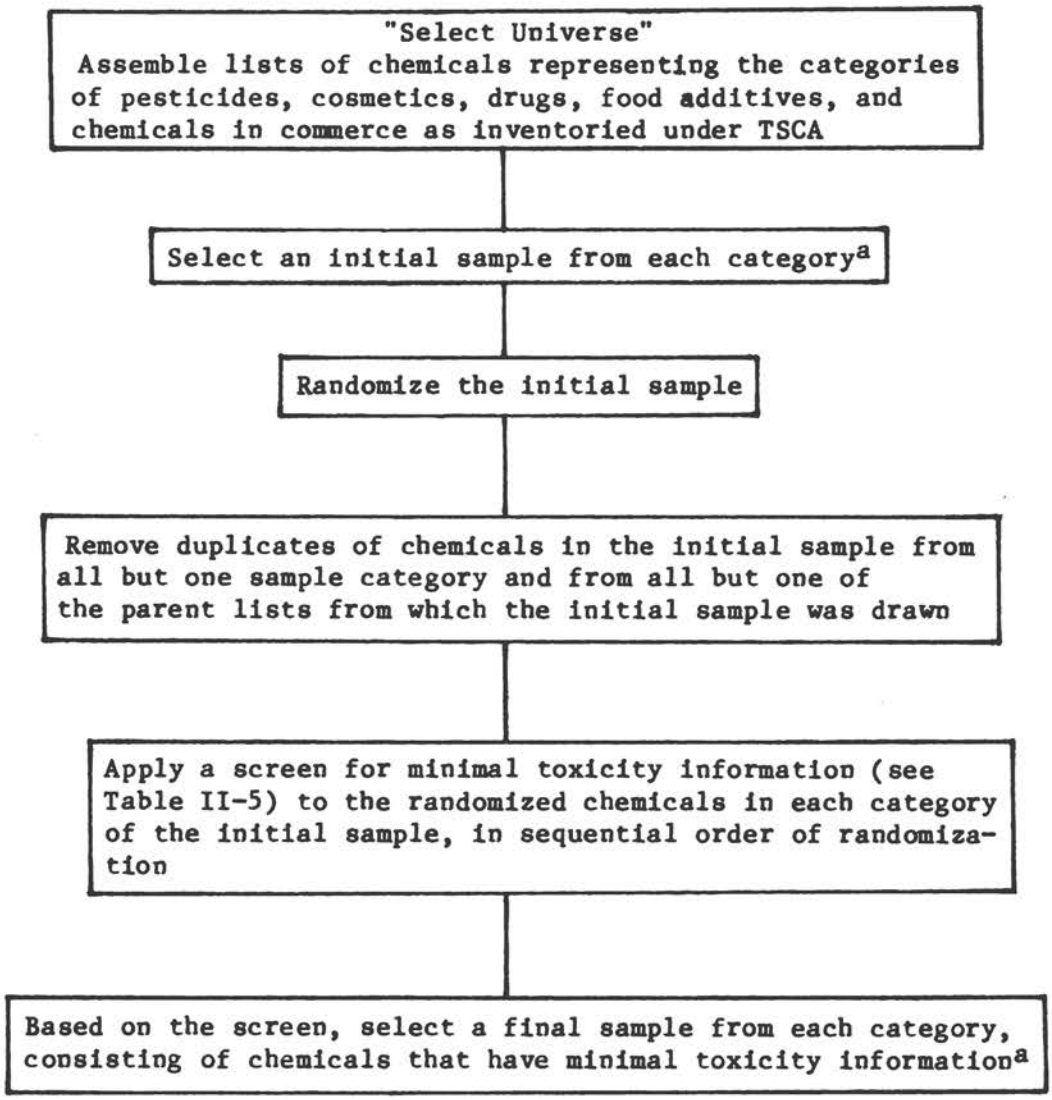

Figure II-1. Process used to draw a sample from the "select universe." Details of each step in the process are described in text.

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[a] See Tables II-1 and II-4 for sizes of the initial and final sample categories

The total universe of chemicals and the "select universe" constantly change under the influence of new chemical syntheses, changes in legislation, and regulatory actions related to use and production. Therefore, the Committee on Sampling Strategies had to draw a sample from a "select universe" that was a snapshot in time; except for the drug category, that sample was so drawn in March 1981. The four sampled categories of the five in the "select universe" were defined by lists that were the most recently updated compilations of chemicals of possible regulatory interest because of their potential human-health hazard. Those lists thus included most of the chemicals that were of interest to NTP. In the selection and manipulation of the sample, the Chemical Abstracts Service (CAS) Registry number was used wherever possible. A small percentage of chemicals in each list did not have assigned CAS Registry numbers, and they were addressed by their chemical names. These and other characteristics of each list are presented in Table II-1. Although the "select universe" was part of a much larger universe of chemicals, its five chemical categories presented, by design, the chemicals of interest for this study.

CHARACTERIZATION OF THE SAMPLING FRAME

The sampling procedure began with the selection and preparation of the lists that most accurately represented the five categories of the "select universe." Each of the four lists examined (the drug list was not included) had its own characteristics that depended on its purposes within the organization for which it was constructed. Thus, there was much variation in content and format. The lists of pesticides, cosmetics, and food additives had characteristics, such as use functions, that were more internally consistent than the characteristics of the TSCA Inventory of chemicals in commerce. They were also smaller. Application of the sampling regimen ultimately chosen by the Committee was therefore easier for those lists than for the list of chemicals in commerce. The characteristics of each category in the "select universe" sampling frame are described below. The numbers describing the sizes of the categories and their components are indicated in Tables II-1 and II-4.

Pesticides

The NIH/EPA Chemical Information System (CIS) lists of registered active pesticides and inert formulation ingredients were used. CIS is a collection of data bases and computer programs to search these data bases. The list of registered active pesticides contains 2,483 entries, including chemicals that at the time of inclusion were for experimental use or that were analogues, salts, or acids of other chemicals in the list. Of the 2,483 entries, 2,218 are unique substances and 256 are duplicate substances on the inert formulation ingredients list. (The EPA has versions of the list that were shortened by clustering chemicals that have similar structural backbones, that are salts or acids of a given chemical, or that are closely related analogues. For the purposes of the sampling exercise

Table II-1. Characteristics of the chemical lists from which the sample was drawn.

Category and Representative Lists	Source	Scope	Organization of List	Year of List	Number of Entries[a]	Number of Chemicals Sampled		
						Total	Initial[b]	Final[c]
Pesticides						3,350	50	15
1. Active Ingredients	EPA	Chemicals that are registered by the EPA for use as pesticides. Some chemicals in the list have pending registrations.	Sequential CAS Registry number	1977	2,218			
2. Registered Inert Ingredients	EPA	Chemicals that are registered by the EPA for use as inert ingredients in pesticide formulations (fillers, solvents, etc.)	Sequential CAS Registry number	1977	867			
Common to both lists					265			
Cosmetics								
3. Chemical dictionary of the Cosmetic, Toiletry and Fragrance Association-	CFTA	Individual ingredients used by the Cosmetics industry.	In three alphabetical cycles	1981		3,410	50	15
Drugs								
4. Bureau of Drugs Ingredient Dictionary	FDA	Prescription drugs, nonprescription drugs, and formulation excipients that are currently in the inventory of the FDA Bureau of Drugs.	- [d]	1981		-[d]	-[d]	15

Table II-1 (continued). Characteristics of the chemical lists from which the sample was drawn.

Category and Representative Lists	Source	Scope	Organization of List	Year of List	Number of Entries[a]	Number of Chemicals Sampled	
					Total	Initial[b]	Final[c]
Food Additives							
5. Bureau of Foods Ingredient Dictionary	FDA	Names of chemicals that are regulated and/or classified by the FDA Bureau of Foods as direct food additives, indirect food additives, GRAS substances, colors and flavors.	Alphabetic	1981	8,627	100	15
Chemicals in Commerce[e]							
6. TSCA:	EPA	Chemicals in commerce in the U.S. over 1,000 lb/yr in 1977.	Sequential CAS Registry number[f]	1978	48,523		
≥1,000,000 lb/yr					12,860	125	10
<1,000,000 lb/yr					13,911	125	10
Unknown/inaccessible production data					21,752	250	20
Total					63,910[g]	700[g]	100

[a] As of March 1981

[b] Each sampled chemical was matched against the chemicals in all originating lists other than the one from which it was derived. Duplicates of chemicals were removed from all but one list according to a procedure described in the section on redundancy in the "select universe." This prevented a chemical from having a greater chance for its selection because it appeared on more than one list. Duplicates were similarly removed from the initial sample. Results of the duplicate removal process are presented in Table II-4.

[c] The initial sample of 700 was reduced to a final sample of 100 by a screening process described in Table II-5.

[d] Undetermined at the time of completion of this report.

[e] Chemicals in commerce, represented by the EPA-Toxic Substances Control Act (TSCA) Inventory, were divided into three categories: (1) Chemicals in production at amounts equal to or greater than 1,000,000 pounds per year, (2) chemicals in production at amounts less than 1,000,000 pounds per per year, and (3) chemicals for which the production levels were unknown or inaccessible because of manufacturers' claims of confidentiality.

[f] CAS Registry numbers were assigned to the chemicals nonselectively as they were received by CAS.

[g] Does not include chemicals in the drug category.

in this study, it was important to maintain the integrity of each chemical by means of its own identity. Therefore, the expanded list of 2,483 entries was used.) The list of registered inert ingredients contains 1,132 ingredients that are present in pesticide formulations but have no claim of pesticidal action. However, because there is the potential for human exposure to pesticide formulation ingredients, the inert ingredients were included in the "select universe." Of the 1,132 entries, 867 are unique substances and 265, as indicated above, are duplicates of substances on the active pesticides list. Removal of duplicate chemicals is described later.

Cosmetics

The list of the Cosmetic, Toiletry and Fragrance Association was used. It contains the names of 3,410 ingredients used in cosmetic formulations--approximately 98% of the raw materials scheduled for publication in the next edition of the CTFA cosmetic-ingredient dictionary. Entries were arranged in three alphabetic cycles, each cycle representing merely the addition of more chemicals to the list in alphabetic order.

Drugs

The Food and Drug Administration's Bureau of Drugs will provide entries from its chemical-ingredient dictionary that include nonproprietary prescription and nonprescription drugs, as well as excipient chemicals used in drug formulations.

Food Additives

The Food and Drug Administration's Bureau of Foods chemical dictionary was used. This dictionary contains 19 chemical sorting codes. Six were used to make up the list of food additives from which the sample was drawn (see Table II-2). The exclusion of a code containing 90 animal drug additives from the food additives category of the "select universe" was discovered after the sample was drawn. The drugs in this code are parent compounds with veterinary applications for animals consumed by humans. Metabolites of these drugs are contained in the chemical name code. Because they were a small fraction of the number of entries in the food additives list, the probability of their selection for the sample was small.

Cosmetic ingredients and drugs in the Bureau of Foods dictionary were specifically excluded from the list used to draw the sample because they were contained in the lists of the cosmetic ingredient and drug categories. The six components used provided a total of 8,627 entries, from which the sample was drawn. An undetermined number of these entries were altered forms of food additives that may appear in foods, even though their presence has not been confirmed by the FDA. These compounds, termed "theoreticals" by the FDA, are

Table II-2. Six codes of chemical classification in the FDA Bureau of Foods dictionary used to form the food additives category from which the food additive sample was drawn.

Code[a]	Fraction of the dictionary[b]
Direct food additives	0.015
Indirect food additives	0.042
Flavors	0.063
Colors	0.003
GRAS[c] substances	0.029
Chemical name[d]	0.174
Total	0.325

[a] Chemicals in 13 codes of the Bureau of Foods chemical dictionary were excluded from the list. The 13 codes were animal drug additives, food additives, biologics, cosmetic label ingredients, cosmetic substances, indirect food additives (temporary file), drugs for human use, industrial chemicals, pesticide chemicals, and trade names for food additives, human-use drugs, pesticides, and veterinary-use drugs.

[b] As of February 4, 1981. The Bureau of Foods dictionary contained 25,401 preferred terms at that time. Each figure represents the fraction of chemicals in the corresponding code file.

[c] Generally Regarded As Safe.

[d] This category contained chemicals that were parts of food additive petitions by manufacturers. Included were substances that (1) were awaiting assignment to a more specific category such as the first five of the Table, or (2) were not assigned a category because they were intermediate products, impurities, or related compounds of safety interest only.

possible products of known chemical pathways. They are not identified by any special designation and could not be removed from the list before sampling. The list was alphabetic with an added minor portion of chemicals whose names began with numeral prefixes; this portion was organized according to ascending value of the numeral prefix. The alphabetic listing precluded separation of ingredients into code categories. Four of the six categories (direct, indirect, color, and flavor additives) implied categorization by use, but the fifth (GRAS) implied a decision by FDA under a "grandfather" clause that all chemicals in this category were not toxic. It was an express desire in this study not to presume the degree of toxicity of any chemical (such as those in the GRAS category), so that sampling could be based strictly on statistical premises and tenets. Therefore, the alphabetic integrity of the list was maintained, and entries in all six categories were allowed to fall as they may.

Chemicals in Commerce

The TSCA Inventory of chemicals in commerce gave rise to special problems because its construction was not restricted by specific use or class, such as drugs, but rather was based on the amount of each chemical produced during 1977, as reported by manufacturers and processors. The Inventory contained (1) chemicals classified into 10 production ranges; (2) a group on which production data were absent; (3) a group on which production data were inaccessible to the general public, because of manufacturers' claims of confidentiality; (4) a group that was not produced during 1977, the year for which production data were amassed to assemble the Inventory; (5) a group used in processing of other substances (as opposed to their own manufacture), on which production data were not obtained; and (6) a group manufactured by trade associations that were not required to report production data under the terms of TSCA. Availability of production data in the Inventory was thus not uniform. This problem was exacerbated by other circumstances surrounding the Inventory's construction:

- Production volumes were reported in ranges too wide to permit accurate summation of volumes of all reporting manufacturers. Furthermore, a manufacturer did not have to report a chemical's production at plant sites where it began after the time of reporting. As a result, the indicated 1977 production of a given chemical may have a large error.
- Under the terms of TSCA, an unknown number of chemical manufacturers, such as small businesses, were not required to report that they were producing a given chemical. This introduced errors of unknown size in the production data in the Inventory on an unknown number of chemicals of unknown identity.

- Processors and users were not required to report. The EPA has estimated that an additional 750,000 report submissions would have resulted without substantially increasing the number of substances.
- Estimates of the total production of petroleum products and related chemicals are not accurately reflected in the Inventory. Although, on the basis of reported production volumes, gasoline is the leading chemical and most of the next 10 high-volume substances are also petroleum products, some chemicals that are major fractions of mixtures are not reported as individual chemicals, but rather are parts of mixtures (e.g., benzene in gasoline).
- Over 85,000 submissions of volume data from manufacturers were not verified by the EPA.
- A given substance may have more than one CAS Registry number in the Inventory.
- About 75% of the known production data are on UVCBs (unknown, variable composition, complex, or biologic), such as petroleum products.
- There are no production data on natural substances, such as asbestos, even though these substances are listed in the Inventory.

The TSCA Inventory was stratified into three categories: chemicals of which 1,000,000 lb or more were produced during 1977, chemicals of which less than 1,000,000 lb were produced during 1977, and chemicals on which production data were inaccessible or absent. These boundaries served two functions:

- They permitted sampling of all chemicals in the Inventory, regardless of whether production data were present.
- Because of the large errors in production levels tabulated in the TSCA Inventory, it did not seem advisable to use the 10 production categories of the Inventory, but rather to group lower-quantity chemicals (less than 1,000,000 lb per year) and not resolve them into finer production categories subject to large errors. For chemicals of which 1,000,000 lb or more were produced per year, errors in reports of production would not seriously affect the outcome of any sampling procedure applied.

The TSCA Inventory contains 48,523 usable entries distributed among the three categories, as shown in Table II-3.

REDUNDANCY IN THE "SELECT UNIVERSE"

The motivation behind the compilation of each list used in the "select universe" varied with the needs of the organization producing the list. Thus, some chemicals appeared in more than one place on the lists defining the "select universe." The sampling plan called for the identification of such duplicates in the sample and their removal from all but one place in the sample. This step would decrease the amount of variance associated with estimates from a sample of fixed size. The statistical procedure did not require the identification of duplicates in the original lists unless they appeared at least once in the sample.

Table II-3. Distribution of TSCA Inventory chemicals among three subcategories.

Subcategory	Number of Entries
≥1,000,000 lb/yr	12,860 (26%)
<1,000,000 lb/yr	13,911 (29%)
Inaccessible/absent production data	21,752 (45%)
Total	48,523

Duplicates appeared at three levels:

- A given chemical might be identified by different names or CAS Registry numbers within a list; this would be an internalized form of redundancy not removed by the organization preparing the list. Although closely related compounds tended to appear on all lists used to define the "select universe," all except the list of active pesticide ingredients had no more than a small amount of intralist redundancy that was statistically tolerable in the sampling process. In one of the extreme instances of intralist redundancy, alkyldimethylbenzylammonium chloride appeared 27 times in the EPA list of active pesticide ingredients, and an analogue of this compound, alkyldimethyl-3,4-dichlorobenzylammonium chloride, appeared 11 times. Intralist redundancy was not removed from the lists.
- The pesticide category consisted of two lists--of active ingredients and of inert ingredients--that were merged into one list before sampling. The lists contained 2,483 active and 1,132 inert ingredients. Removal of redundancy during the computer merging process (there were 265 duplicates) yielded a pesticide category of 3,350 chemicals.
- Some chemicals appeared on more than one of the lists forming the "select universe" because they were of interest to more than one of the organizations from which the lists originated. As examples of this interlist redundancy, some pesticides became indirect food additives because of their presence as residues in food for human consumption, and some chemicals were used both as food additives and as cosmetic ingredients.

Instances of the latter two forms of redundancy were removed before sampling. The two lists of pesticide ingredients were voided of duplicated chemicals, but no attempt was made to remove intralist redundancy, because it was slight. The third form of redundancy (interlist redundancy) was adjusted for after the drawing of the sample. The tally of duplicate chemicals arising from this source was small, and the original composition of the lists and the sizes of samples drawn from them had to be altered only slightly.

Interlist redundancy was removed according to a sampling hierarchy developed by the Committee on Sampling Strategies for the four sampled categories of the "select universe." The hierarchy reflected the sampling rate from each list. Thus, a list that was smaller and therefore had the higher sampling rate retained duplicated sampled chemicals.

In this way, the established hierarchy for removal of duplicate chemicals became (from high to low), pesticides, cosmetics, drugs (to be included when it is sampled), food additives, and chemicals in commerce. A sampled chemical that appeared more than once in the sample was stricken from the lists of all categories in which it appeared, except the highest in the hierarchy. This process reduced the untreated "select universe" from 63,910 to 63,798 (without drugs). Although it removed duplicates of sampled chemicals that were present on more than one list, it did not account for duplicates

not selected in the sampling process. Therefore, duplicates unassociated with the sample were still contained in the various lists making up the "select universe." The composite breakdown of this reduction is presented in Table II-4. During later analysis of data on the sample, inferences with respect to the entire "select universe" will include estimates of further reductions because of the failure of duplicates to fall into one or another part of the sample.

This process also reduced the initial sample size from 700 to 696 (without drugs). Two compounds had to be deleted from the initial sample of 50 pesticides--one that was erroneously placed by the EPA in its active-ingredients list from which the sample was drawn, and one that appeared twice in the sample of 50 as a result of redundancy within the same active-ingredients list. One food additive had to be deleted from the sample because it also appeared in the pesticide sample; in this instance, cosmetics were higher in the hierarchy and thereby retained the duplicated chemical. Likewise, one chemical was removed from the chemicals-in-commerce sample because it also appeared in another category of the sample with a higher priority.

CONSIDERATIONS IN DEVELOPING THE SAMPLING STRATEGY

The development of a sampling plan almost inevitably involves a series of compromises. For example:

- Will the most important inferences apply to the whole population, to independent segments of it, or to comparisons among segments?
- Can the sampling frame be defined in a way that is simultaneously precise and focused on the real objects of inquiry?
- What part of the total effort will be devoted to preparation of the lists from which the sample will be drawn?
- Does the difficulty of data collection vary substantially from one population member to another, and, if so, should the variation be used to reduce total costs (or expand sample size within a fixed budget)?

In the present case, these and similar questions were particularly acute because of the great cost and effort required for each substance to be subjected to full investigation and assessment.

The Committee believes that the sampling plan it adopted provides for a reasonable and workable set of compromises among the competing demands and constraints already noted. However, three issues require additional discussion:

- The effects of the small total sample size.
- The partition of the sample among the various lists and sublists.
- The handling of interlist duplicates.

Table II-4. Removal of duplicates of chemicals from the sample and lists representing the "select universe."[a]

Category in the hierarchy	"Select Universe"		Initial sample	
	Original	With duplicates removed	Original	With duplicates removed
Pesticides	3,350	3,350	50	48
Cosmetics	3,410	3,410	50	50
Drugs	_b	_b	_b	_b
Food additives	8,627	8,613	100	99
Chemicals in commerce:				
≥1,000,000 lb/yr	12,860	12,826	125	125
<1,000,000 lb/yr	13,911	13,898	125	125
Unknown/inaccessible production level	21,752	21,701	250	249
Total	48,523	48,425	500	498
Total[c]	63,910	63,798	700	696

[a] The relationship of the initial sample indicated in this table to the final sample of 100 chemicals is presented in Table II-1.

[b] Undetermined.

[c] Does not include chemicals from the drug category.

In assessing the sample size, one should remember that some of the most important information (presence or absence of minimal toxicity data) will be collected on many substances, and that the detailed study is limited only to 100 substances (this number and all other numbers used in this section are explained below). Furthermore, the 100 substances should be adequate to make sufficiently reliable inferences regarding the total "select universe." It is only when one wishes to examine small parts of the "select universe" that serious problems arise. For example, a simple random sample of 100 chemicals drawn directly from the "select universe" might be expected to yield about five pesticides, but there is no assurance that the luck of the draw would actually provide even this many. Such a sample would be inadequate for usable inferences about pesticides. The Committee therefore decided to sacrifice some precision in estimates for the whole population (a compromise reflected in larger expected variances on population-wide estimates) so as to have larger numbers in a few subcategories of special interest (with substantially smaller expected variances of estimates for those subcategories). Although fixed sample sizes of 10, 15, and 20 clearly will not permit inferences of high precision, this tradeoff was deemed by the Committee to be optimal.

In light of the same considerations, the Committee believed that the 15:15:15:15:40 division of available effort, and the further 10:10:20 split of the 40 substances from the TSCA Inventory, would allow at least minimal inferences regarding specific subcategories, roughly in proportion to the need for information on their toxicity. These samples are probably at the lower limit of sample sizes that are usable for the present purposes; to make some groups larger at the expense of other groups would have meant the elimination of the latter from separate consideration. (Of course, they would still have contributed to inferences regarding the whole of the "select universe.")

Some substances appear on more than one of the lists used to define the "select universe." Such duplicates could have been identified in the whole universe or only for substances in at least one of the subsamples; once identified, they could have been left in place or removed. There would be little statistical advantage, but much effort, in a careful matching of the entire lists, in that appropriate techniques of data analysis can use the frequency and distribution of duplicates actually appearing in the sample to estimate and adjust for the effects of duplicates in items not sampled. The advantage of having precise, rather than estimated, numbers of duplicates was judged not to offset the extra cost and effort of matching the entire lists.

The efficient analysis of subcategories of the "select universe" would require identification of at least the duplicates appearing in the sample. However, there is much merit in the notion that they should not be, in effect, removed from all but one list as the sample is drawn, inasmuch as such substances are likely to be of special interest because of their broader use.

For present purposes, the Committee concluded that there were even greater advantages in removing such duplications. The reasons include the small number of duplicates expected (insufficient for separate study), the general balance between inferences for the whole "select universe" and those for subsets, the lack of precise information on whether the presumption of wider use (and risk) of these substances was valid, and some simplification of the analysis and presentation of results.

SAMPLE SIZE

Both the sampling plan and the sample size were substantially affected by the large resource investment needed to study a subset of the sample. Investigation of chemicals in the sample was a two-stage process: initial screening (rapid and inexpensive) to determine whether toxicity studies had been performed and reported, followed by a detailed search (resource-intensive) for information on chemicals for which there were reported studies. It appeared that not more than 100 chemicals could be assessed in the latter step, and preliminary studies suggested that a sample size of 700 would produce at least 100 chemicals for the later detailed study.

Fixing of the sample size and division of the total among the five lists were also contingent on a number of other aspects of the lists from which the sample was drawn, including human resource limitations.

The initial sample of 700 (696 with duplicates removed) was selected to determine an estimate of the proportion of chemicals on whose toxicity there is published material. The final sample of 100 was selected to provide 100 chemicals with at least minimal toxicity information, so that its quality could be assessed. Not all 696 were screened to find chemicals with toxicity information. The estimates of the proportions with information presented later are based on the number screened to find the required 100.

The proportionate representation of the five categories in the final sample of 100 chemicals was determined largely by the sizes of the various lists from which the sample was being drawn, with care not to impose any idea of regulatory preference of one category over another. As illustrated in Table II-4, the size of the TSCA Inventory of chemicals in commerce that was used is about 6-14 times as large as the other lists. It therefore received a greater representation than any other list. With the decision to weight the sample size of the other four categories equally, it became necessary to fix appropriate sizes for chemicals in commerce in relation to the other four categories. The Committee regarded the 15:15:15:15:40 (pesticides:cosmetics:drugs:food additives:chemicals in commerce) distribution in the final sample of 100 illustrated in Table II-1 to be a reasonable allocation of the effort.

Early in its deliberations, the Committee considered a direct drawing of a random sample of 100 chemicals from a "select universe" of 63,910. This approach was rejected because such a sample would probably not include enough chemicals from lists of the pesticides,

cosmetics, drugs, and food additives to permit inferences regarding those lists. On the basis of a mock sampling exercise that was conducted in part to determine the proportion of chemicals in the "select universe" likely to have toxicity information, the Committee decided that an initial sample of 700 drawn from the "select universe" would provide a bank of chemicals from which a representative 100 with some toxicity data could be drawn. Information from the mock sampling indicated that the 700 chemicals should be distributed among the five categories of the "select universe" in a proportion of 50:50:50:50:500 (pesticides:cosmetics:drugs:food additives:chemicals in commerce).[a] From these 700 the final sample of 100 with at least minimal toxicity information would be drawn according to the proportion of 15:15:15:15:40. These numbers were altered slightly in the process of removing redundancy. Furthermore, on the basis of the division of the TSCA Inventory into three production categories (see Table II-3), the 500 chemicals of the initial sample were divided into 125 chemicals produced at 1,000,000 lb/yr or more, 125 produced at less than 1,000,000 lb/yr, and 250 in the unknown-inaccessible group. Drawn from these were the 40 chemicals for the final sample: 10, 10, and 20, respectively.

SAMPLING PLAN

SELECTION OF THE ELEMENTS

The Committee chose a sampling mechanism that would satisfy the following requirements:

- The size of the final sample was limited by resources available to evaluate the toxicity information on each chemical in the sample. The limit of resource capability was set at 100 compounds in this sample.
- The final sample was to contain representatives of all five categories of chemicals of interest to the NTP--i.e., all chemicals in the "select universe." This included pesticides, cosmetics, drugs, food additives, and chemicals in commerce.
- A stratified sampling was used to control the composition of the sample with respect to the five categories in the "select universe." This was particularly critical in an attempt to draw samples from all categories in such a way as to glean information from each. For example, the list representing chemicals in commerce, the TSCA Inventory, although larger than the other lists, has a disproportionately small number of chemicals with toxicity information, compared with the drug and pesticide categories, which, by regulation, must have toxicity information associated with their use before registration and marketing. Variations in the toxicity data bases of chemicals in the five categories resulting from different degrees of exposure to them was considered by the Committee to be a second reason for choosing a stratified sampling procedure. By stratifying according to these five categories, it was possible to specify adequate numbers of chemicals from all lists.

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[a] The initial sample of 50 food additives was used up before a final sample of 15 with minimal toxicity information could be selected from it. Therefore, 50 more food additives were added to the initial sample so that the proportions became 50:50:50:100:500 (pesticides:cosmetics:drugs:food additives:chemicals in commerce). The 50 drugs were not part of the 700 chemicals in the initial sample referred to in this report.

SAMPLING REGIMEN

The "select universe" contained 63,798 chemicals. The Committee determined that an initial sample of 696 without chemicals from the drug category (700 before removal of redundancy) should be drawn from the "select universe" in a manner that reflected the sizes of the five categories.

The sample was drawn by using one procedure five times--once for each category. The procedure was to select the sixteenth chemical in a list (from a combination of two lists in the case of the pesticides and the twelfth chemical in the case of the 50 supplemental food additives) as the first sampled substance. The sixteenth (or twelfth) position was chosen from a table of random numbers. The rest of the chemicals in the category being sampled were drawn from the remainder of the list at equal intervals, the fixed size of the interval and number of intervals chosen to use the entire list in obtaining the required number of chemicals in the category being sampled. Thus, the sample was drawn from all parts of each list. This procedure, called "systematic sampling with a random start," is standard in such applications. Because the interval varied among the lists, the sampling rate was not the same. This gave rise to a disproportionate sample. However, because a method of probability sampling was applied to each list, the sample was still statistically valid and useful.

The Committee paid special attention to the systematic (nonrandom) nature of this phase of sampling, but was convinced that each list was in itself effectively random, at least over relatively short ranges. The likelihood of important bias from this step was judged to be negligible. Possible effects on the variance of estimates were also judged to be small.

After the selection of the 696 chemicals, each entry in each category was assigned a random number. These numbers, each with its assigned chemical, were numerically ordered within each category, to provide five randomly ordered samples totaling 696.

The plan called for a screening of a random subset of the chemicals initially sampled for minimal toxicity information. This served two functions:

- In the assessment of the adequacy of toxicity testing by the Committee on Characterization of Status of Toxicity Data Elements for a Select Universe of Compounds (commonly called the Committee on Toxicity Data Elements), screening precluded the appearance in the final sample of a chemical on which there was no toxicity information or only a modicum of such information--too little for use by that Committee.
- In the ensuing search of the literature for all available toxicity information, screening obviated wasted exhaustive searching for literature when none was present.

The determinants for minimal toxicity information presented in Table II-5 were laid out by the Committee on Toxicity Data Elements. That Committee deemed that up to five types of study--acute, chronic, subchronic, genetic, and reproductive (or teratologic)--applied to the

Table II-5. Required studies (*) in the screen to extract from the initial sample of 696 chemicals a final sample of 85 with minimal toxicity information.

Study Type[a]	Category: Pesticides[b]	Cosmetics[c]	Drugs[d]	Food Additives[e]	Chemicals in Commerce
1. Acute toxicity (by any route) single administration within 24 hours	*	*	*	*	If any two study types were present, the chemical became a member of the final sample
2. Subchronic toxicity studies (oral, dermal 28-d, 90-d, including guinea pig sensitization)	*	*	*	*	If all chemicals in the initial sample failed to meet the standard in searching for the required 40, then the standard was to be lowered so that information in one study type was sufficient to qualify as minimal toxicity information[f]
3. Reproductive toxicity and/or teratogenicity			*	*	
4. Chronic toxicity studies				*	
5. Genetic toxicity					

[a] Human case studies and experiments with humans were included in these five study types.

[b] If information was present in the two specified study types and any one of the three remaining study types, the chemical became a member of the final sample of 15.

[c] If information was present in the two specified study types, the chemical became a member of the final sample of 15.

[d] In the later drug sampling, if information is present in the three specified study types, the chemical will become a member of the final sample of 15.

[e] If information was present in any three of the four specified study types, the chemical became a member of the final sample of 15.

[f] Based on an examination of 30 chemicals, it was projected that two study types would not be found for a sufficient number of chemicals in the entire initial sample of chemicals in commerce (all three production categories). Therefore, as indicated, the standard was lowered so that only one study type was sufficient for the chemical to meet minimal toxicity information requirements.

chemicals of the five categories of the "select universe" might be necessary to constitute minimal toxicity information. With the terms outlined for each category in Table II-5 as a guideline, the randomly ordered chemicals in the sample were screened for this minimal information according to their randomly ordered appearance in their own categories. This proceeded until the predetermined number with minimal toxicity information for the final sample was reached. In the process of achieving the current final sample size of 85 without the 15 drugs (15:15:15:40), chemicals that the literature search revealed to be below the minimal standard were dropped from the list.

The limited-search strategy used in screening had three steps:

- The Chemical Information System (CIS) Structure and Nomenclature Search System (SANSS) was searched to find alternative names of the chemical in question and to point to other data bases where information on that chemical might be found.
- If CIS did not provide information on alternative chemical names or other data bases, the National Library of Medicine's Chemline and the Chemical Abstracts Service data base were searched for such information.
- Once the location of available information was ascertained, the following sequence was implemented in an attempt to acquire minimal toxicity information on a chemical:

  -- The Registry of Toxic Effects of Chemical Substances (RTECS) and the Toxicology Data Base (TDB) were searched for basic toxicity information (skin irritation, eye irritation, LD_{50}, LC_{50}, TD_{LO}, etc.).

  -- If the minimal information requirement was not met by searching RTECS and TDB, the National Library of Medicine's Toxline was searched for information on acute, chronic, subchronic, genetic, and reproductive (or teratogenic) toxicity.

  -- If the requirement still was not met, the Toxicology Information Center of the National Academy of Sciences was searched.

  -- If the reqirement still was not provided by all preceding parts of the search strategy, two source books were used.

Whenever the requirement for minimal toxicity information was met, the search for information on the chemical in question ended. Three chemical indexes used in this search (CIS SANSS, the National Library of Medicine's Chemline, and the Chemical Abstracts Service's Chemname) collectively contain over 5 million unique chemical substances that are identified by CAS Registry numbers, with synonyms and trade names for each chemical. RTECS and TDB offer toxicity data extracted from published research findings. Toxline houses 11 subfiles, including those generated for Chemical-Biological Activities (CBAC), Air Pollution and Industrial Hygiene, Toxicity Bibliography (TOXBIB), Abstracts on Health Effects of Environmental Pollutants (HEEP), Pharmaceutical Abstracts, Pesticides Abstracts, Environmental Mutagen

and Environmental Teratology Information Center files, and the Toxicology Section of Chemical Abstracts. These contain literature from 1965 to the present. For literature published from 1950 to 1965, the Toxicology Information Center's card catalog was searched manually.

In this manner, 85 chemicals constituting a final sample with minimal toxicity information as prescribed by the Committee on Toxicity Data Elements were selected from a larger initial, randomly ordered, stratified sample of 696, which itself was a product of a larger "select universe" of 63,910 chemicals that are of interest to the NTP. These figures will increase according to the sizes of the drug list and the initial and final drug samples.

Under the direction of the Committee on Toxicity Data Elements, the sample of 100 will be subjected to an exhaustive literature search in the assessment of toxicity testing by that Committee.

Discussion of several critical aspects of statistics are reserved for a later report of this study when some results of the sample investigation will be available. These include bias in the sample, statistical power for the most critical comparisons, and variances of estimators. These discussions will include mathematical formulas and methods where appropriate.

THE SAMPLE

Two samples were generated with the procedure described above. An initial sample of 696 chemicals was derived from the lists representing the four sampled categories of the "select universe" (see Appendix II-1). This sample was drawn to provide an estimate of the proportion of chemicals on which there was minimal toxicity information. A final sample of 85 chemicals was derived from the initial sample of 696. This sample was drawn to provide an estimate of the proportion of chemicals with available toxicity information so that its quality could be examined.

The four categories in the initial sample had distinguishing characteristics that reflected their origins and the intended uses of their members. Most of the 50 chemicals in the pesticide sample were organic. Several entries in this category were not unique single-substance chemicals, but rather constituents of composite materials (e.g., soap bark), organisms (e.g., Agrobacterium radiobacter), deliberate mixtures (e.g., trinitrobenzene-aniline complex), substances structurally related to other substances in the same sample [e.g., acetic acid, (2,4-dichlorophenoxy)-, compound with 1,1',1''-nitrilotris(2-propanol), structurally similar to 2,4-dichlorophenoxyacetic acid, alkylamine salt], and mixtures of at least partially unspecified composition (e.g., alkyldimethyl-benzylammonium chloride).

Although chemicals in the cosmetic ingredient category also tended to be organic, there were more mixtures, synthetic polymers, long-chain hydrocarbons, and extracts of foods. The specification of ingredients required by the FDA Bureau of Drugs is expected to result in clearly identifiable chemical entities in the drug category of the sample.

The food-additive category contained a variety of organic, inorganic, and composite materials (e.g., yeast extract, geranium oil, fennel, asafetida oil, butter fat, and celery seed extract). The category of chemicals in commerce had an even wider array of organic, inorganic, and composite materials that included complexes and mixtures. This is because that portion of the "select universe" contained chemicals with unspecified use patterns or unspecified routes of human exposure.

The final sample (see Appendix II-1) reflects the characteristics of the randomized initial sample. The initial sample size of 696 was adequate to obtain 85 with minimal toxicity information.

On the basis of the list in Appendix II-1, 34, 41, and 67 chemicals in each of the three categories of pesticides, cosmetics, drugs, and food additives in the initial sample had to be screened to locate 15 chemicals with minimal toxicity information for the final sample. In the category of chemicals in commerce, 84, 32, and 58 chemicals had to be screened to obtain the required 10, 10, and 20 for the final sample. Thus, minimal toxicity information was found on 21 - 42% of the pesticides, cosmetics, and food additives in the lists used in sampling, and 11 - 33% of the chemicals in the TSCA Inventory (see Table II-6). Standard errors ranged from 3 to 8%.

Table II-6. Characteristics of results of the search for minimal toxicity information associated with chemicals in the initial sample of 696.

Category	Number of chemicals examined (A)	Number of chemicals with minimal toxicity information (B)	Estimate of the per cent with minimal toxicity information[a]	Standard error of the per cent
Pesticides	34	15	42	8
Cosmetics	41	15	35	8
Drugs	-[b]	15	-[b]	-[b]
Food Additives	67	15	21	5
Chemicals in Commerce				
≥1,000,000 lb/yr	84	10	11	3
<1,000,000 lb/yr	32	10	29	8
Unknown/inaccessible production data	58	20	33	6

[a] With the sampling procedure used, dividing column B by column A results in a biased estimate of the proportion with minimal toxicity information. An unbiased estimate is made by subtracting 1 from both the numerator and the denominator of the numbers in column A and B (Kendall and Stuart, 1973).

[b] The drug sample had not been taken at the time of completion of this report.

SUMMARY AND CONCLUSIONS

The principal objective of the Committee on Sampling Strategies was to devise a method for drawing a sample from the universe of chemicals that are of interest to the National Toxicology Program. The need of the NTP and the committees of this study for a sampling procedure is based on the fact that determining the toxicity-testing needs of more than 70,000 chemicals of interest to the NTP, if derived from an assessment of each of these chemicals, would far exceed the resource limitations of the NTP and the committees.

An approximation to the chemical universe of interest to the NTP--the "select universe"--was used as the sampling frame for which the Committee on Sampling Strategies developed a sampling procedure. Five major categories--pesticides, cosmetics, drugs, food additives, and chemicals in commerce--were considered to encompass the majority of chemicals to which humans are exposed.

Each of the five operational categories was defined by chemical lists developed by various organizations. Collectively, the lists of the pesticides, cosmetics, food additives, and chemicals-in-commerce categories (not including drugs) formed a chemical dictionary of 63,910 compounds, mixtures, organisms, and composite materials that constituted the "select universe" in this study. This was reduced to 63,798 after the removal of duplicate chemicals.

A maximal final sample size of 100 chemicals to study the quality of the toxicity information on each was considered to be the limit of resource capability in determining the adequacy of toxicity testing and the testing needs for the "select universe." The Committee on Sampling Strategies determined that a double-sample, stratified, random sampling procedure was most appropriate to the sampling frame and the intended uses of the sample. These three characteristics were the guidelines in the development of the sampling method.

The lists of chemicals were kept intact in the four sampled strata of the sampling frame, from each of which a portion of the sample was drawn. This was considered necessary to permit some minimal analysis of the characteristics of each list. First, 696 chemicals were drawn from the "select universe" to form the initial sample. Then, a screening process was applied to a random subset of these 696 chemicals on which minimal toxicity information, as defined by the Committee on Toxicity Data Elements, was sought to identify 85 chemicals (15 drugs will be identified later). Random ordering of the initial sample before its screening was designed to eliminate order effects within the lists representing the five categories.

The sampling procedure developed by the Committee on Sampling Strategies was applied to the "select universe" after duplicate chemicals were removed to the extent practical. Chemicals for the initial sample of 696 were taken from all areas in all lists. The part of the initial sample apportioned to each of the four categories took account of the relative sizes of the categories in the larger "select universe" from which the sample was drawn, as well as the relative degrees of interest and the relative likelihood of finding minimal toxicity information. The final sample of 100 chemicals was designed to contain 15 pesticides, 15 cosmetic ingredients, 15 drugs, 15 food additives, and 40 chemicals in commerce (10 produced at

1,000,000 lb/yr or more, 10 at less than 1,000,000 lb/yr, and 20 at rates that were unknown or inaccessible because of manufacturers' claims of confidentiality).

Eighty-five of the 100 chemicals in the sample have been selected. The pesticides are largely organic, but many are composites, organisms, deliberate mixtures, or substances that are structurally related to other substances in the sample, or are at least partially unspecified in composition. The cosmetic ingredients tend to be organic mixtures, synthetic polymers, long-chain hydrocarbons, and food extracts. The food additives are organic, inorganic, and composite materials. Chemicals in commerce have a similar array of variations in composition.

A range of 21 - 42% of the pesticides, cosmetics, and food additives and a range of 11 - 33% of the chemicals in commerce in the initial sample that were passed through the screening process for minimal toxicity information met minimal standards. That may reflect the proportions of chemicals with minimal toxicity information in the same categories in the much larger "select universe."

Statistical methods used in the analysis and rationales for choice of methods will be discussed in a later report of this study.

REFERENCE

Kendall, M., and A. Stuart. 1973. The Advanced Theory of Statistics. 3rd ed., Vol. 2, p. 614. New York: Hafner Publishing Company.

Appendix II-1

Initial sample of 696 chemicals and final sample of 85 chemicals from the "select universe."

The 696 chemicals in the initial sample and their CAS Registry numbers are listed below in randomly ordered sequence within the four categories of pesticides, cosmetics, food additives, and chemicals in commerce. Those of the initial sample that have been selected for the final sample of 85 are noted by an asterisk (*) denoting that they had minimal toxicity information. The selection process ceased where a solid line appears because the required number for the final sample were found. CAS Registry numbers have not been determined for those chemicals where blank spaces appear.

PESTICIDES

Number	Chemical	CAS number
1	Ammonium ligninsulfonate	8061-53-8
2	*[2,2,2-Trichloro-1-hydroxyethyl) dimethyl= phosphonate]	52-68-6
3	*Alkyldimethylbenzylammonium chloride	8001-54-4
4	S-tert-Butyl dipropylthiocarbamate	2212-63-7
5	Soap bark	
6	*1,2,4-Thiadiazole, 5-ethoxy-3-(trichloromethyl)-	2593-15-9
7	1-Butanesulfonothioic acid, 5-(chloromethyl) ester	16008-31-4
8	*Phenol, 4-(di-2-propenylamino)-3,5-dimethyl-, methylcarbamate (ester)	6392-46-7
9	Sulfonated oleic acid, potassium salt	
10	*2H-1,3,5-Thiadiazine-2-thione, tetrahydro-3,5-= dimethyl-	533-74-4
11	Phosphoric acid, tributoxyethyl ester	36441-71-3 78-51-3
12	Sodium decyldiphenyletherdisulfonate	
13	Trichlorobenzyl chloride	1344-32-7
14	Benzenecarbothioamide, 2,5-dichloro-	69622-81-7
15	*Citric acid, trisodium salt	68-04-2
16	Aniline-1,3,5-trinitrobenzene 1:1 complex	3101-79-9
17	*Ethylene thiourea	96-45-7
18	Acetic acid, (2,4-dichlorophenoxy)-, compound with 1,1',1"-nitrilotris[2-propanol]	32341-80-3
19	*4,4'-Bipyridinium, 1,1'-dimethyl-, dichloride	1910-42-5
20	Alpha-Butoxy-omega-hydroxy ethylene oxide-= propylene oxide copolymer	9038-95-3
21	*Potassium iodate	7758-05-6

Number	Chemical	CAS number
22	*Cobalt chloride ($CoCl_2$), compound with pyridine	110-86-1
23	Chlormethylfos	24934-91-6
24	*2,3,5-Trichloro-4-(propylsulfonyl)pyridine	38827-35-9
25	*p-Benzoquinone	106-51-4
26	(2-Hydroxyethyl)ethylenediaminetriacetic acid, trisodium salt	139-89-9
27	2-Propanamine, sulfate	60828-92-4
28	*p-Nitrophenyldimethylthionophosphate	297-97-2
29	2,4-Dichlorophenoxyacetic acid, alkylamine salt	
30	*Sodium acetate	127-09-3
31	Agrobacterium radiobacter	
32	3-Methyl-1-phenylpyrazol-5-yl dimethylcarbamate	87-47-8
33	Carbonic acid, methyl 2-(1-methylheptyl)-4,6-= dinitrophenyl ester	5386-68-5
34	*Phosphorodithioic acid, O,O-dimethyl ester, S-ester with N-(mercaptomethyl)phthalimide	732-11-6
35	C.I. Pigment green 21 (Copper acetoarsenite, solid)	12002-03-8
36	p-Benzoquinone, 2,3,5,6-tetrachloro-	118-75-2
37	Tolylmercuric acetate	1300-78-3
38	Copper hydroxide ($Cu(OH)_3$)	20427-59-2
39	Acetic acid, (2,4-dichlorophenoxy)-, methyl-2-[methyl-2-[methyl-2-(2-methylpropoxy)ethoxy]ethoxy]ethyl ester	53535-28-7
40	Bis(5,10-dihydrophenarsazine) oxide	4095-45-8
41	Benzoic acid, 2-hydroxy-, compound with 4-chloro-benzenamine (1:1)	53404-66-3
42	Polyoxyethylenepolyoxypropylenemonoisopropanolamide of caprylic acid	
43	Heptadecenylimidazoline	
44	o-Dichloroaniline	27134-27-6
45	Zinc sulfate monohydrate	7446-19-7
46	Sodium pentaborate	
47	1H-Imidazo[4,5-b]pyridine, 6-chloro-2-= (trifluoromethyl)-	13577-71-4
48	[1,1'-Biphenyl]-2-ol, ammonium salt	52704-98-0

Number	Chemical	CAS number
1	Poloxamine 1301	11111-34-5
2	Sucrose benzoate/sucrose acetate isobutyl	12738-64-6
		126-13-6
3	Acetylated lanolin ricinoleate	977055-85-8
4	Peg-70 hydrogenated lanolin	68648-27-1
5	*Maleic acid	110-16-7
6	Pareth-91-8	68439-46-3
7	Methylpropylcellulose	977057-25-2
8	Safflower glyceride	977058-10-8
9	Peg-30 glyceryl oleate	68889-49-6
10	Octadecene/maleic anhydride copolymer	25266-02-8
11	*FD&C Red No. 40	25956-17-6
12	*Ammonium phosphate	7722-76-1
13	PPG-8-Ceteth-10	9087-53-0
14	*4,4'-Isopropylidenediphenol	80-05-7
15	*Ethyl linolenate	1191-41-9
16	Allantoin calcium pantothenate	4207-41-4
17	Nonoxynol-8	26027-38-3
		37205-87-1
18	*Calcium acetate	62-54-4
19	Sucrose benzoate	12738-64-6
20	Laureth-3	3055-94-5
21	Potassium oleate	143-18-0
22	*Peg-100 stearate	9004-99-3
23	Cocamine oxide	61788-90-7
24	Sodium myristyl sulfate	1191-50-0
25	*Tetrasodium EDTA	64-02-8
26	Cetearyl alcohol	8005-44-5
27	Dimethyl cocamine	61788-93-0
28	*p-Cresol	106-44-5
29	*DM Hydantoin	77-71-4
30	Isosteareth-6 carboxylic acid	
31	*Dehydroacetic acid	520-45-6
32	Spinach extract	
33	Benzophenone-11	1341-54-4
34	*Peg-200	25322-68-3

Number	Chemical	CAS number
35	*Guanidine carbonate	593-85-1
36	PPG-2 methyl ether	13429-07-7
		37286-64-9
37	D&C Orange No. 5 zirconium lake	977054-31-1
38	Hydrogenated tallow amine oxide	61788-94-1
39	*Sodium bromate	7789-38-0
40	Barium sulfide	21109-95-5
41	*Oleth-15	9004-98-2
		25190-05-0
42	Phloroglucinol	108-73-6
43	Zinc myristate	16260-28-8
44	Acetylated glycol stearate	
45	Vinylpyrrolidone/vinyl acetate/itaconic	68928-72-3
46	Sorbitan triisostearate	54392-27-7
47	Peg-14 oleate	9004-96-0
48	Honey extract	
49	Quaternium-8	977066-07-1
50	Trisodium EDTA	150-38-9

DRUGS[a]
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[a] The drug list had not been received from the FDA at the time of completion of this report.

Number	Chemical	CAS number
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Number	Chemical	CAS number
1	Mannose	31103-86-3
2	Acetamidobenzoic acid, p	556-08-1
3	Vanadium tetrachloride	7632-51-1
4	Ethyl 3-hydroxybutyrate	5405-41-4
5	2,7-Dinitroso-1-naphthol	977014-63-3
6	Fennel (Oil 8006-84-6)	
7	*Norharman	244-63-3
8	Ionone, gamma	79-76-5
9	Triethylamine hydrochloride	554-68-7
10	*Cupric sulfate, anhydrous	7758-98-7
11	Ammonium thiocyanate	1762-95-4
12	Yeast extract, baker's	8013-01-2
13	Dimethylphenylpiperazinium iodide	54-77-3
14	Sulfide ion	18496-25-8
15	Allyl nonanoate	7493-72-3
16	Geranium oil	8000-46-2
17	Benzyl thiocyanate	3012-37-1
18	Polyvinyl ethyl ether	25104-37-4
19	Elemene alpha	5951-67-7
20	Methyl isobutyate	547-63-7
21	*Jasmine absolute	8031-01-4
22	*Calcium stearate	977050-22-8
23	Pentaerythritol tetrakis(3-mercaptopropionate)	7575-23-7
24	Propyl 2-furanacrylate	623-22-3
25	Butter fat	977018-87-3
26	CI Fluorescent brightener #109	61951-68-6
27	Soybean mill feed	977030-55-9
28	Cobalt(2+) caprylate	1588-79-0
29	Tetramethyl tin	594-27-4
30	Chromous oxide	12018-00-7
31	*1-Monostearin	123-94-4
32	Asafetida oil	977017-80-3
33	*Hydrazine hydrate	7803-57-8
34	DI-Dodecyl tin oxide	2273-48-5
35	Molybdic acid	11099-00-6
36	Celery seed extract	

Number	Chemical	CAS number
37	Diethylene glycol dibenzoate	120-55-8
38	p-Menth-1-en-9-ol	18479-68-0
39	*Sodium lauryl sulfate	151-21-3
40	Guanidoethyl cellulose	9069-21-0
41	Lipase, animal	977033-78-5
42	Silicon	7440-21-3
43	2-Ethylhexyl 9,10-epoxystearate	141-38-8
44	*1,4-Dihydroxy-9,10-anthraquionine	81-64-1
45	Phytoene	540-04-5
46	Isoamyl isobutyrate	2050-01-3
47	2-Tridecanone	593-08-8
48	N-Tert-butylacrylamide	107-58-4
49	*Riboflavin supplement	977030-53-7
50	*Acenaphthylene	20-89-68
51	Mannide monoleate	25399-93-9
52	*Di-(2-methoxylethyl)phthalate	117-82-8
53	*Diethylene glycol	111-46-6
54	*Linseed oil	8001-26-1
55	Artichoke leaf	
56	N-Stearoylsarcosine	142-48-3
57	Ethyl 2-methylbutyrate	7452-79-1
58	Chromium hydroxide	12626-43-6
59	Xylyl sulfone	27043-27-2
60	p-Cymen-8-ol	1197-01-9
61	Molybdate orange	12656-85-8
62	Ammonium Isovalerate	7563-33-9
63	Feculose starch acetate	977033-03-6
64	Rhynchosia pyramidalis	977030-08-2
65	Cobalt tallate	61789-52-4
66	*Sodium laureth-3 sulfate	13150-00-0
67	*Silica	7631-86-9
68	Elaidic acid	112-79-8
69	2-Tert-butyl-4-ethylphenol	96-70-8
70	Allyl isovalerate	2835-39-4
71	1-Methylpiperozinc	109-01-3
72	Calcium saccharin	6381-91-5
73	Polyvinyl chloride	9002-86-2

Number	Chemical	CAS number
74	Isoamyl cinnamate	7779-65-9
75	Benzyl phenylacetate	102-16-9
76	Sulfasomidine	
77	Butirosin sulfate	51022-98-1
78	Guaiaretic acid	500-40-3
79	Soybean hull, ground	977032-85-1
80	Norbixin	542-40-5
81	Triethyl lead	5224-23-7
82	Propyl phenol	31019-46-2
83	Humulus	977001-58-3
84	Phthalocyanine	574-93-6
85	Cupric hydroxide	20427-59-2
86	Cedarwood oil terpene	68608-32-2
87	C.I. Disperse orange #3	730-40-5
88	1,4-Dianilinoanthraquinone	2944-12-9
89	Dimethylol melamine	5001-80-9
90	Tetrakis(hydroxymethyl)phosphonium chloride	124-64-1
91	2-Ethylhexyl mercaptoacelate	7659-86-1
92	Pentaerythritol monostearate	78-23-9
93	Itaconic acid-methyl methacrylate copolymer	27155-24-4
94	2,6,6-Trimethyl-2-cylclohexen-1-one	20013-73-4
95	Geranial	141-27-5
96	3,4,5,6-Dibenzacridine	224-53-3
97	Ion-exchange membrane	
98	Methyl hydrogen siloxane	63148-57-2
99	Valproic acid	99-66-1

CHEMICALS IN COMMERCE

Production level ≥1,000,000 lb/yr

1	7-Oxabicyclo[4.1.0]heptan-2-one,6-methyl-3-(1-methylethyl)-	5286-38-4
2	2-Pyrazolin-5-one, 1-(p-aminophenyl)-3-ethoxy-	4105-91-3
3	Bismuth, compound with gadolinium (1:1)	12010-44-5
4	Benzene, (2-iodoethyl)-	17376-04-4
5	Molybdenum phosphide (MoP)	12163-69-8

Number	Chemical	CAS number
6	D-Glucose, enzyme-hydrolyzed	68921-30-2
7	Thiazole, 2-(2-methylpropyl)-	18640-74-9
8	1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl)= ester, polymer with 1,3-diisocyanatomethyl= benzene, methyloxirane and 1,2,3-propanetriol	68492-79-5
9	Amines, N,N,N'-trimethyl-N'-tallow alkyltrimethyl= enedi-	68783-25-5
10	2-Propenoic acid, butyl ester, polymer with ethenyl acetate=and 2-hydroxyethyl 2-= propenoate	65776-73-0
11	Poly(oxy-1,2-ethanediyl), .alpha.,.alpha.'-[ethylocta= decyliminio)di-2,1-ethanediyl]bis[.omega.-= hydroxy-, ethyl sulfate	42845-62-5
12	1,7-Naphthalenedisulfonic acid, 4-[(2,4- dichlorobenzoyl)amino]-5-hydroxy-6-[(2-methoxy= phenyl)azo]-,disodium salt	6416-33-7
13	*Benzenesulfinic acid, 4-chloro-	100-03-0
14	1,2-Benzenediamine, N-methyl-, dihydrochloride	25148-68-9
15	Bismuth hydroxide	10361-43-0
16	*Ethanol, 2-[[2-[(2-aminoethyl)amino]ethyl]= amino]-	1965-29-3
17	Phenol, 4,'4-(3H -2,1-benzoxathiol-3-ylidene)= bis[2,5-dimethyl]-, S,S-dioxide	125-31-5
18	Benzenethiol, 4-dodecyl-, hydrogen phosphoro= dithioate, zinc salt	65045-85-4
19	*Isoquinoline, 1,2,3,4-tetrahydro-	91-21-4
20	*Pentanamide, N,N-dimethyl-	6225-06-5
21	2-Propenamide, N-(hydroxymethyl)-, polymer with 1,3-butadiene and 2-propenenitrile	26603-98-5
22	*9H-Fluorene, 2-nitro	607-57-8
23	Tannins, salts with 2-[3-(1,3-dihydro-1,3,3-trimethyl= 2H-indol-2-ylidene)-1-propenyl]-1,3,3-trimethyl-= 3H-indolium	68957-25-5
24	Benzenepropanoic acid, 4-[bis[2-(benzoyloxy)ethyl]= amino]-,.alpha.,.beta.-dicyano-, ethyl ester	65151-61-3
25	Silane, (3-isocyanatopropyl)trimethoxy)-	15396-00-6
26	Benzenesulfonic acid, 3-[(ethoxycarbonyl)amino]-, monosodium salt	71215-93-5

Number	Chemical	CAS number
27	Hexanedioic acid, polymer with methyloxirane polymer with oxirane ether with oxybis[propanol] (2:1)	63549-52-0
28	Octanoic acid, mixed esters with triethylene glycol hexanoate	68130-48-3
29	Benzene, 1-iodo-3-nitro-	645-00-1
30	Calcium hydroxide, reaction products with iron oxide (Fe_2O_3) and magnesium hydroxide	68411-13-2
31	1-Propanaminium, N-ethyl-N,N-dimethyl-3-[(1-oxoeicosyl)=amino]-, ethyl sulfate	67846-22-4
32	8-Oxa-3,5-dithia-4-stannaundecan-1-ol, 4,4-dimethyl-9-=oxo-,propanoate	67905-21-9
33	Poly(oxy-1,2-ethanediyl), .alpha.-[2,4-bis(2-phenyl-1-=propenyl)phenyl]-.omega.-hydroxy-	72088-88-1
34	2-Naphthalenesulfonic acid, 7-amino-5-[[4-[(2-bromo-1-=oxo-2-propenyl)amino]-2-[(4-methyl-3-sulfophenyl)=sulfonyl]phenylazo]-, disodium salt	70210-02-5
35	Acetamide, N,N'-1,3-propanediybis-, N-[3-C_{20-30}-=(alkyloxy)propyl]derivatives	70528-81-3
36	Benzene, 1,1'-[1,2-ethanediylbis(thio)]bis-	622-20-8
37	2-Naphthalenesulfonic acid, 6-[2,6-dimethylphenyl)=amino]-4-hydroxy-	23973-67-3
38	1-Propanamine, 2-chloro-N,N-dimethyl-, hydrochloride	4584-49-0
39	Ethanone, 1-(2,4,5-triethoxyphenyl)-	63213-29-6
40	Acetonitrile, 2,2',2'',2'''-(1,2-ethanediyldinitrilo)=tetrakis-	5766-67-6
41	*Carbamic acid, (4-chlorophenyl)-, 1-methylethyl ester	2239-92-1
42	2,4,6(1H,3H,5H)-Pyrimidinetrione, 5-phenyl-1-(phenyl=methyl)-	72846-00-5
43	Yttrium oxide sulfate, ytterbium-doped	68585-88-6
44	Didymium (rare earth mixture)	8006-73-3
45	Ethanol, 2,2'-oxybis-, polymer with .alpha.-hydro-=.omega.-hydroxypoly(oxy-1,4-butanediyl) and 1,1'-=methylenebis[4-isocyanatobenzene]	64078-69-9
46	*Benzene, 1,2,3,5-tetramethyl-	527-53-7
47	Phenol, isooctyldinitro-	37224-61-6
48	1,3,-Naphthalenedisulfonic acid, 7-[[4-[[4-[(4-amino=benzoyl)amino]-2-methylphenyl]azo]-2-methyphenyl]=azo]-, disodium salt	6949-09-3

Number	Chemical	CAS number
49	Hexanedioic acid, dimethyl ester, polymer with N,N'-bis(2-aminoethyl)-1,2-ethanediamine and dimethyl pentanedioate	72175-31-6
50	Bicyclo[3.1.0]hex-2-ene, 2-methyl-5-(1-methylethyl)-	2867-05-2
51	Benzo[a]phenoxazin-7-ium, 9-dimethylamino)-, chloride	966-62-1
52	*Acetic acid, chloro-, 2-phenylethyl ester	7476-91-7
53	Antimony phosphide (SbP)	25889-81-0
54	Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-, ether with 2-[(2-hydroxyethyl)amino]-2-(hydroxymethyl)-1,3-propanediol (4:1)	72269-66-0
55	Iron, complexes with diazotized 2-amino-4,6-dinitrophenol monosodium salt coupled with diazotized 4-amino-5-hydroxy-2,7-naphthalenedisulfonic acid, diazotized 4-amino-3-methylbenzenesulfonic acid, diazotized 4-nitrobenzenamine and resorcinol	71662-50-5
56	Glycerides, tallow di-	68553-08-2
57	1,3-Isobenzofurandione, polymer with 1,2-ethanediol, 2,5-furandione and 2,2'-oxybis[ethanol]	28679-80-3
58	2-Naphthalenesulfonic acid, 5-[bis(methylsulfonyl)amino]-1-[(methylsulfonyl)oxy]-, sodium salt	58596-06-8
59	2-Butenedioic acid (E)-, polymer with 1,3-butadiene, ethenylbenzene, (1-methylethenyl)benzene, methyl 2-methyl-2-propenoate and 2-propenenitrile	69898-51-7
60	Phosphonic acid, [1,6-hexanediylbis[nitrilobis(methylene)]]tetrakis-, hexammonium disodium salt	68298-90-8
61	Vanadic acid ($H_4V_2O_7$), teracesium salt	55343-67-4
62	Cyclohexanone, 2,6-dimethyl-4-(3-methylbutyl)-	71820-43-4
63	Oxirane, methyl-, polymer with oxirane, mono(hydrogen sulfate), tridecyl ether	70850-89-4
64	Oils, menhaden, polymers with benzoic acid, glycerol and isophthalic acid	68458-39-9
65	Benzenesulfonic acid, 2,5-dichloro-4-[4-[[3-[[3-[[1-(2,5-dichloro-4-sulfophenyl)-4,5-dihydro-5-oxo-1H-pyrazol-4-yl]azo]benzoyl](phenylmethyl)amino]-4-methylphenyl]azo]-4,5-dihydro-5-oxo-1H-pyrazol-1-yl], disodium salt	71050-54-9
66	1H-Purine-2,6,8(3H)-trione, 7,9-dihydro-, calcium salt	827-37-2
67	Vanadium silicide (V_3Si)	12039-76-8

Number	Chemical	CAS number
68	Formaldehyde, polymer with methylphenol and 1,3,5,7-tetraazatricyclo[3.3.1.1^{3,7}]decane	68845-06-7
69	Coal, sulfonated	69013-20-3
70	2,5-Hexanediol, 2,5-dimethyl-	110-03-2
71	1(3H)-Isobenzofuranone, 3,3-bis[4-(sulfooxy)phenyl]-, dipotassium salt	52322-16-4
72	Benzene, 1,2,4-trichloro-3-(chloromethyl)-	1424-79-9
73	Ethanone, 2-(acetyloxy)-1,2-diphenyl-	574-06-1
74	1H-Isoindol-1-one, 3-amino-	14352-51-3
75	Poly(difluoromethylene), .alpha.-hydro-.omega.-[(Phosphonooxy)methyl]-	72987-44-1
76	Poly[oxy(methyl-1,2-ethanediyl)], .alpha.-hydro-.omega.-[[[[3[[[2-(1-aziridinyl)ethoxy]carbonyl]amino]methylphenyl]amino]carbonyl]oxy]-, ether with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (3:1)	68015-74-7
77	[1,1'-Binaphthalene]-,8,8'-dicarboxylic acid	29878-91-9
78	1H-Isoindole-5-carboxylic acid, 2,3-dihydro-1,3-dioxo-	20262-55-9
79	Terpenes and Terpenoids, Litsea cubela-oil, hydrogenated	68608-36-6
80	[1,1'-Bicyclohexyl]-2-carboxylic acid, 4',5-dihydroxy-2',3-dimethyl-5',6-bis[(1-oxo-2-propenyl)oxy]-, methyl ester	67952-52-7
81	*Ethene, (2,2,2-trifluoroethoxy)-	406-90-6
82	Acetamide, N-[2-(acetyloxy)ethyl]-	16180-96-4
83	Chromate(3-), [3-hydroxy-4-[(2-hydroxy-1-naphthalenyl)azo]-7-nitro-1-naphthalenesulfonato(3-)][4-hydroxy-3-[[[2-hydroxy-5-[[4-(phenylazo)phenyl]azo]phenyl]methylene]amino]benzenesulfonato(3-)]-, trisodium	72479-29-9
84	*Stannane, difluorodimethyl-	3582-17-0
85	Butanedioic acid, bis(2-mercaptoethyl) ester	60642-67-3
86	Starch, 2,3-dialdehydo	9047-50-1
87	2-Propenoic acid, 2-methyl-, 2-ethyl-2[[(2-methyl-1-oxo-2-propenyl)oxy]methyl]-1,3-propanediyl ester, polymer with ethenylbenzene, chloromethylated, trimethylamine-quaternized	68908-37-2
88	Benzene, 1,2-dichloro-4-(trichloromethyl)-	13014-24-9

Number	Chemical	CAS number
89	Cyclopentanone, 2-(3-methyl-2-butenyl)-	2520-60-7
90	1,3-Benzenedicarbonyl dichloride, 5-hydroxy-	61842-44-2
91	Acetic acid, (4-formylphenoxy)-	22042-71-3
92	Ethanaminium, N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-= propenyloxy]-, chloride, polymer with 2-propenamide and N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propenyl)= oxy]ethanaminium methyl sulfate	68227-15-6
93	4(1H)-Pyrimidinone, 6-hydroxy-	1193-24-4
94	Phenol, 4,4'-(1-methylethylidene)bis-, polymer with N,N'-bis(2-aminoethyl)-1,2-ethanediamine and (chloro-= methyl)oxirane, nonylphenol-modified	68951-48-4
95	Naphthalenesulfonic acid, dibutyl-, ammonium salt	68379-06-6
96	1,4-Benzenedicarboxylic acid, dimethyl ester, polymer with dimethyl pentanedioate, 1,6-hexanediol and 2,2'-= oxybis[ethanol]	71519-81-8
97	Resin acids and Rosin acids, hydrogenated, esters with diethylene glycol	68648-51-1
98	Benzenesulfonic acid, 5-chloro-2,4-dinitro-	56961-56-9
99	Cyclohexane, isocyanato-	3173-53-3
100	Triethylenetetramine, polymer with ethylene oxide	31510-83-5
101	Pyrazineethanethiol	35250-53-4
102	1,4-Benzenedicarboxylic acid, polymer with 1,3-dihydro-= 1,3-dioxo-5-isobenzofurancarboxylic acid, hexanedioic acid and 1,2-propanediol	70729-94-1
103	Fatty acids, castor-oil, polymers with cottonseed-oil fatty acids, dehydrated castor-oil fatty acids, glycerol, phthalic anhydride and soya fatty acids	68525-89-3
104	2-Propenoic acid, 2-methyl-, 3-(trimethoxysilyl)= propyl ester, polymer with N-(1,1-dimethyl-3-oxobutyl)-= 2-propenamide, ethenyl acetate and 2-ethylhexyl 2-propenoate	67785-57-3
105	Iron, complexes with 2-ethylhexanoic acid and tall-oil fatty acids	68187-36-0
106	Uranium bromide (UBr_4)	13470-20-7
107	Hexanoyl chloride	142-61-0
108	Benzeneethanol, .alpha.-butyl-, acetate	40628-77-1
109	Cyclotrisiloxane, hexamethyl-, polymer with (1,1-= dimethylethyl)ethenylbenzene and (1-methylethenyl)= benzene	66836-92-8

Number	Chemical	CAS number
110	1,2-Benzenedicarboxylic acid, compound with benzenamine (1:1)	50930-79-5
111	Imidodisulfuric acid, ammonium salt	27441-86-7
112	Benzenamine, N,N-dimethyl-4-[[4-(methylamino)-phenyl]methyl]-	53477-27-3
113	Zinc, chloro[[2,2''-nitrilotris[ethanolato]](1-)-N,O,O',O'']-	33520-38-6
114	Uranium fluoride (UF_5)	13775-07-0
115	Safflower oil, polymer with glycerol and TDI	68072-09-3
116	Poly(oxy-1,2-ethanediyl), .alpha.,.alpha.'-[(docosylimino)d:-2,1-ethanediyl]bis[.omega-hydroxy-	38796-84-8
117	Cyclopentanecarboxylic acid, 1-amino-	52-52-8
118	Benzenediazonium, 5-[(butylamino)sulfonyl]-2-methoxy-, (T-4)-tetrachlorozincate(2-) (2:1)	62778-15-8
119	3-Butenal, 2,3-dimethyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-	68140-49-8
120	Fatty acids, C_{5-10}, esters with polypentaerythritol	68915-66-2
121	2-Propenoic acid, 2-methyl-, C_{7-18}-alkyl esters, polymer with 2-[methyl[(.gamma.-.omega.-perfluoro-C_{8-14}-alkyl)sulfonyl]amino]ethyl 2-methyl-2-propenoate	68988-55-6
122	Alcohols, C_{6-12}, ethoxylated	68439-45-2
123	2-Propenoic acid, 2-chloro-, methyl ester	80-63-7
124	Benzene, 1-methyl-4-phenoxy-	1706-12-3
125	1-Propanaminium, N-ethyl-N,N-dimethyl-3-[(2-methyl-1-oxo-2-propenyl)amino]-, ethyl sulfate	70942-19-7

Production level <1,000,000 lb/yr

1	1-Hexene, 6-chloro-	928-89-2
2	Formaldehyde, polymer with phenol and 3a,4,7,7a-tetrahydro-4,7-methano-1H-indene	29862-25-7
3	4,7-Methano-1H-indenecarboxaldehyde, octahydro-	30772-79-3
4	Hexadecanoic acid, octadecyl ester	2598-99-4
5	Poly(oxy-1,2-ethanediyl), .alpha.-(1-oxo-2-propenyl)-.omega.-methoxy-	32171-39-4
6	*2-Propenoic acid, 2-methyl-, 2-hydroxypropyl ester, homopolymer	25703-79-1

Number	Chemical	CAS number
7	1H-Benzimidazole, 5-chloro-2-methyl-	2818-69-1
8	Silane, bicyclo[2.2.1]hept-2-yltrichloro-	18245-29-9
9	Pyridinium, 1-[2-[p-[(2-cyano-4-nitrophenyl)azo]-N-= ethylanilino]ethyl]-, chloride	23258-43-7
10	*Furanmethanol, tetrahydro-, phosphate (3:1)	10427-00-6
11	m-Dioxane, 2,5,5-trimethyl-2-propyl-	5421-99-8
12	Silicic acid ($H_4Si_4O_4$), tetraphenyl ester	1174-72-7
13	Benzamide, 4-methoxy-3-nitro-N-phenyl-	97-32-5
14	Indol-3-ol, dihydrogen phosphate (ester), disodium salt	3318-43-2
15	*1-Propanaminium, N,N,N-tripropyl-, bromide	1941-30-6
16	Heptanoic acid, anhydride	626-27-7
17	*Nitrous acid, 3-methylbutyl ester	110-46-3
18	*Dextran, hydrogen sulfate	9042-14-2
19	Azulene, 1,2,3,4,5,6,7,8-octahydro-1,4-dimethyl-7-= (1-methylethylidene)-, (1S-cis)-	38-84-6
20	Silane, 1,4-phenylenebis[chlorodimethyl-	1078-97-3
21	Formic acid, rubidium salt	3495-35-0
22	*Butanedioic acid, tetrafluoro	377-38-8
23	Glycols, polyethylene, hydrogen sulfate, eicosyl ether, sodium salt	26636-38-4
24	*Silane, dichloroethenylethyl-	10138-21-3
25	*2,8,9-Trioxa-5-aza-1-silabicyclo[3.3.3]undecane, 1-= methyl-	2288-13-3
26	Methanediamine, dihydrochloride	57166-92-4
27	*Ichthammol	8029-68-3
28	Benzenediazonium, 4,4'-(1,2-ethenediyl)bis[3-sulfo-, dichloride	13954-62-6
29	D-Arabinitol	488-82-4
30	Phosphate(1-), hexafluoro-, ammonium	16941-11-0
31	Platinum, dichloro[1,2,5,6-.eta.)-1,5-cyclooctadiene]-	12080-32-9
32	*Terbium oxide	12738-76-0
33	1H-Benzotriazolecarboxylic acid reated	60932-58-3
34	Hexanoic acid, decyl ester	52363-43-6
35	Docosanoic acid, 3-hydroxy-2,2-bis(hydroxymethyl)= propyl ester	53161-46-9
36	Ethanol, 2,2,2-trifluoro-, 4-methylbenzenesulfonate	433-06-7
37	Ethanol, 2-methoxy-, sodium salt	3139-99-9

Number	Chemical	CAS number
38	Benzene, 1-(chloromethyl)-2,4-dimethyl-	824-55-5
39	2-Butenoic acid, 2-methyl-, butyl ester, (Z)-	7785-64-0
40	1,6-Hexanediamine, N,N'-dibutylidene-	1002-91-1
41	Benzenesulfonamide, N,4-dimethyl-	640-61-9
42	2-Naphthalenecarboxylic acid, 5-(acetylamino)-1-= hydroxy-	63133-78-8
43	9,10-Anthracenedione, 1,4-bis[(2,6-diethylphenyl) amino]-	20241-74-1
44	Ethanesulfonyl chloride, 2-chloro-	1622-32-8
45	1H-1,2,4-Triazol-3-amine, 5-(methylthio)-	45534-08-5
46	Benzamide, N-hydroxy-N-phenyl-	304-88-1
47	Phosphonic acid, dodecyl-, diethyl ester	4844-38-6
48	Iridium oxide	1312-46-5
49	9-Octadecenoic acid (Z)-, methyl ester, sulfurized, copper-treated	61788-34-9
50	2-Propenoic acid, ethyl ester, polymer with ethenylben-= zene, formaldehyde and 2-propenamide	28650-65-9
51	1H-3a,7-Methanoazulene, octahydro-3,8,8-trimethyl-6-= methylene-, [3R-(3.alpha.,3a.beta..7.beta.,8a.= alpha.)]-	546-28-1
52	1,2-Propanediol, 3-[(2-hydroxyethyl)thio]-	1468-40-2
53	Lead ruthenium oxide	37194-88-0
54	2-Butenedioic acid (Z)-, mono(2-ethylhexyl) ester, polymer with ethenyl acetate and 2-ethylhexyl 2-propenoate	61909-78-2
55	2,3b-Methano-3bH-cyclopenta[1,3]cyclopropa[1,2]= benzene-4-methanol, octahydro-7,7,8,8-tetramethyl-	59056-64-3
56	Benzenemethanesulfonic acid, .alpha.,4-dihydroxy-= 3-methoxy-, monosodium salt	19473-05-3
57	1,2-Ethanediamine, N,N'-bis(1,1-dimethylethyl)-	4062-60-6
58	2-Propenal, 2-methyl-3-[2-(1-methylethyl)phenyl]-	6502-23-4
59	9,12-Tetradecadien-1-ol, (Z,E)-	51937-00-9
60	Hexanoic acid, 2,2,3,3,4,4,5,6,6,6-decafluoro-5-= (trifluoromethyl)-	15899-29-3
61	1,3-Benzenedicarboxylic acid, polymer with 2,5-= furandione, 1,6-hexanediol and 1,2-propanediol	42133-48-2
62	Butanamide, N-(3-aminophenyl)-3-oxo-, monohydrochoride	59994-21-7
63	Acetic acid, sec-octyl ester	54515-77-4

Number	Chemical	CAS number
64	Trisiloxane, 1,1,1,3,5,5,5-heptamethyl-3-[(trimethylsilyl)oxy]-	17928-28-8
65	Benzenepropanol, 4-(1,1-dimethylethyl)-.beta.-methyl-	56107-04-1
66	Benzoic acid, 2-hydroxy-, strontium salt (2:1)	526-26-1
67	2-Propenoic acid, diester with butanediol	31442-13-4
68	Acetamide, 2-chloro-2,2-difluoro-	354-28-9
69	Docosanoic acid, octadecyl ester	24271-12-3
70	3-Cyclohexene-1-carboxaldehyde, dimethyl-	27939-60-2
71	2-Propenoic acid, 3-(1H-imidazol-4-yl)-	104-98-3
72	Propanedinitrile, [[3-chloro-4-(octadecyloxy)phenyl]hydrazon, 6-hexanediol and 1,2-propanediol	41319-88-4
73	Phenol, 4,4'-(2-pyridinylmethylene)bis-, diacetate (ester)	603-50-9
74	1-Butanesulfonic acid, 4-[(4-aminophenyl)butylamino]-	35079-64-2
75	Benzoic acid, 4-[1-[[[5-[[4-[2,4-bis(1,1-dimethylpropyl)phenoxy]-1-oxobutyl]amino]-2-chlorophenyl]amino]carbonyl]-3,3-dimethyl-2-oxobutoxy]-, methyl ester	63217-24-3
76	Propanoic acid, 3-chloro-2,2-dimethyl-	13511-38-1
77	Butane, 2,2-dichloro-	4279-22-5
78	2-Propenoic acid, 2-methyl-, polymer with N-(butoxymethyl)-2-propenamide, butyl 2-propenoate, ethenylbenzene and ethyl 2-methyl-2-propenoate	36089-48-2
79	3-Thiazolidineacetic acid, 5-[(3-ethyl-2-thiazolidinylidene)ethylidene]-4-oxo-2-thioxo-	21155-21-5
80	Octadecanamide, N-[3-(dimethylamino)propyl]-, monoacetate	13282-70-7
81	L-Ascorbic acid, 6-hexadecanoate	137-66-6
82	2-Propenoic acid, 2-methyl-, 2-aminoethyl ester, hydrochloride	2420-94-2
83	2,4,7,9-Tetraazadecanediimidamide, 3,8-diimino-, sulfate (1:2)	62708-53-6
84	2-Propenoic acid, 2-methyl-, 2-ethoxyethyl ester, polymer with 2-hydroxyethyl-2-methyl-2-propenoate	29403-23-4
85	Benzoic acid, 2-sulfo-, monoammonium salt	6939-89-5
86	Silane, dichloroethyl-	1789-58-8
87	1-Butanol, germanium(4+) salt	25063-27-8
88	2,7-Naphthalenedisulfonic acid, 6-amino-4-hydroxy-3-[[7-sulfo-4[(4-sulfophenyl)azo-1-naphthalenyl]azo]-, tetrasodium salt	2118-39-0

Number	Chemical	CAS number
89	Benzeneethanol, 4-methyl-	699-02-5
90	Silane, trichlorodocosyl-	7325-84-0
91	1-Propanamine, 3,3'-[1,2-ethanediylbis(oxy)]bis-	2997-01-5
92	Cyclohexanemethanol, 4-amino-.alpha.-(4-amino-cyclohexyl)-, carbamate (ester)	15484-34-1
93	Benzene, nitroso-	586-96-9
94	Propanoic acid, ethenyl ester, polymer with 1-ethenyl-2-pyrrolidinone	26124-21-0
95	7-Dodecyn-1-ol, acetate	16504-87-3
96	4-Hexanal, 5-methyl-2-(1-methylethyl)-	58191-81-4
97	Benzothiazole, 2,2'-dithiobis-, compound with zinc chloride (1:1)	22405-83-0
98	2-Pentyn-1-ol	6261-22-9
99	Cycloheptanone, 2-chloro-	766-66-5
100	1,3-Dioxane, 2,4,5-trimethyl-4-phenyl-	37922-18-2
101	3-Pyridinecarbonitrile, 2,6-bis[2-hydroxyethyl)-amino]-4-methyl-	38841-88-2
102	Decanoic acid, 1-methyl-1,2-ethanediyl ester	53824-77-4
103	Phosphoric acid, copper(2+) salt (2:1)	18718-12-2
104	Cadmium zinc sulfide	11129-14-9
105	Ethanol, 2-methoxy-, triester with boric acid (H_3Bo_3	14983-42-7
106	2-Propanol, 1-(2-hydroxyethoxy)-3-(2-propenyloxy)-	33065-62-2
107	Ethanone, 1-(3-nitrophenyl)-	121-89-1
108	Benzene, 1,1'-sulfonylbis[2,4-dimethyl-	5184-75-8
109	1,4-Benzenediamine, N^4-ethyl-N^4-(2-methoxyethyl)-2-methyl-, bis(4-methylbenzenesulfonate)	50928-80-8
110	Glycine, N,N'-1,2-ethanediylbis-	5657-17-0
111	Propanenitrile, 3-[1-phenyl-1H-tetrazol-5-yl)thio]-	3061-46-0
112	1,2-Ethanediamine, N-[(4-methoxyphenyl)methyl]-N',N'-dimethyl-N-2-pyridinyl-, monohydrochloride	6036-95-9
113	Benzoic acid, 3-amino-, methyl ester	4518-10-9
114	3H-Pyrazol-3-one, 2,4-dihydro-5-[(4-nitrophenyl)-amino]-2-(2,4,6-trichlorophenol)-	34320-82-6
115	Nitric acid, ytterbium(3+) salt	13768-67-7
116	Benzoic acid, 3,5-diamino-4-chloro-, butyl ester	40362-35-4
117	Ethanamine, N-ethyl-N-nitroso-	55-18-5
118	Phosphonium, tetrakis(hydroxymethyl)-, acetate (salt)	7580-37-2

Number	Chemical	CAS number
119	Benzamide, 2-(acetyloxy)-N-(4-chlorophenyl)-3,5-diiodo-	14437-41-3
120	2-Propanone, 1-(1-hydroxycyclohexyl)-	25290-13-5
121	Silane, trichloro(dichlorophenyl)-	27137-85-5
122	Heptadecanoic acid, potassium salt	17378-36-8
123	1(3H)-Isobenzofuranone, 3,3'-bis(3,5-dibromo-4-hydroxyphenyl)-	76-62-0
124	1-Penten-3-ol	616-25-1
125	2-Naphthalenesulfonic acid, 8-hydroxy-5,7-dinitro-, barium salt (1:1)	55482-31-0

Unknown/inaccessible production level

1	2-Propanone, 1-(2-furanyl)-	6975-60-6
2	*1-Hexadecen-3-ol-3,7,11,15-tetramethyl-	505-32-8
3	Phenol,dodecyl-, lead(2+) salt	68586-21-0
4	Poly(oxy-1,2-ethanediyl), .alpha.-[2,4-bis(1-methylpropyl)phenyl]-.omega.-hydroxy-	67970-22-3
5	2,7-Naphthalenedisulfonic acid, 4-amino-6-[[4-[[[4-[(2,4-diaminophenyl)azo]phenyl]amino]sulfonyl]phenyl]azo]-, 5-hydroxy-3-[(4-nitrophenyl)azo]-	72089-20-4
6	Fatty acids, tall-oil, polymers with glycerol, maleic anhydride, phthalic anhydride and soybean oil	68015-41-8
7	Benzoic acid, 2-hydroxy-5-[(4-nitrophenyl)azo]-, monosodium salt	1718-34-9
8	Safflower oil, polymer with conjugated safflower oil, glycerol, methyl methacrylate, pentaerythritol, phthalic anhydride and styrene	68083-08-9
9	Propanoic acid, 3,3'-thiobis-, diethyl ester	673-79-0
10	*Distillates (petroleum), solvent-dewaxed light paraffinic	64742-56-9
11	Poly(oxy-1,2-ethanediyl), .alpha.-(carboxymethyl)-.omega.-hydroxy-, C_{12-13}-alkyl ethers	70750-17-3
12	Trisiloxane, 1,1,1,5,5,5-hexamethyl-3-phenyl-3-[(trimethylsilyl)oxy]-	2116-84-9
13	2-Propenoic acid, 2-methyl-, methyl ester, polymer with ethenylbenzene, 2-propenenitrile and 2-propenoic acid	38684-13-8

Number	Chemical	CAS number
14	Quarternary ammonium compounds, bis(hydrogenated tallow alkyl)dimethyl, methyl sulfates	61789-81-9
15	Manganese alloy, base, Mn 65-68,Fe 10-23,Si 12-21, C 0.5-3,P 0-0.2 (ASTM A483)	12743-28-1
16	*Germanium	7440-56-4
17	2-Propenenitrile, polymer with 1,3-butadiene and ethenylbenzene, ammonium salt	67952-85-6
18	Phenol,4-(2,4-dichlorophenoxy)-	40843-73-0
19	*Lithium, (1-methylpropyl)-	598-30-1
20	Oils, menhaden, polymers with p-tert-butylphenol, formaldehyde, glycerol, pentaerythritol, phthalic anhydride and rosin	68553-68-4
21	6-Octenoic acid, 3,7-dimethyl-, methyl ester	2270-60-2
22	*Propanal, 2-methyl-	78-84-2
23	Ethanaminium, N-[4-[[4-(diethylamino)phenyl][4-=(ethylamino)-1-naphthalenyl]methylene]-2,5-=cyclohexadien-1-ylidene]-N-ethyl-, tri-=hydroxypentatriacontaoxo[phosphato(3-)]dodeca-=molybdate(4-) (4:1)	69070-64-0
24	*1,3-Propanediol, 2-methyl-2-[(nitrooxy)methyl]-, dinitrate (ester)	3032-55-1
25	*2,6,10,14,18,22-Tetracosahexaene, 2,6,10,15,19,23-=hexamethyl-, (all-E)-	111-02-4
26	*Benzene, 1,1'-oxybis[2,3,4,5,6-pentabromo-	1163-19-5
27	2-Propenoic acid, polymer with ethenylbenzene, ethyl 2-propenoate, formaldehyde and 2-propenamide	67846-51-9
28	2,7-Naphthalenedisulfonic acid, 4-hydroxy-3-[[4-[[2-(sulfooxy)ethyl]sulfonyl]phenyl]azo]-, tripotassium salt	72187-37-2
29	*1-Pentan-3-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)	127-42-4
30	Fatty acids, C_{12-18}, polymers with adipic acid, C_{14-18} fatty acids, 1,6-hexanediol, isodecanol and propylene glycol	71060-65-6
31	*Bicyclo[7.2.0]undec-4-ene, 4,11,11-trimethyl-8-methyl=ene-, [1R-(1R*,4E,9S*)]-	87-44-5
32	*Vanadic acid, ammonium salt	11115-67-6
33	2-Propanethiol	75-33-2
34	1-Octacosanol	557-61-9
35	*Carbonic acid, nickel(2+) salt (1:1)	3333-67-3

Number	Chemical	CAS number
36	*Ferrocene	102-54-5
37	Soybean oil, polymer with isophthalic acid and trimethylolethane	66070-63-1
38	Tin hydroxide	12054-72-7
39	*C.I. Pigment Green 7	1328-53-6
40	*Zeolites, calcium-iron-magnesium-vanadium-containing	68918-02-5
41	Glycine, N-phenyl-, monosodium salt	10265-69-7
42	*tert-Dodecanethiol	25103-58-6
43	2-Anthracenesulfonic acid, 1-amino-9,10-dihydro-4-=[[4-[(methylamino)methyl]phenyl]amino]-9,10-=dioxo-, monosodium salt	67905-55-9
44	Benzenemethanol, .alpha.-ethynyl-.alpha.-methyl-	127-66-2
45	Fatty acids, tall-oil, polymers with dipropylene glycol, maleic anhydride and pitch	68459-12-1
46	*Acetaldehyde, chloro-	107-20-0
47	Fatty acids, tall-oil, compounds with N-methyldicyclo-=hexylamine	68188-05-6
48	Benzenesulfinic acid, methyl-, bis[4-(dimethylamino)=phenyl]methyl ester	29061-52-7
49	*Zinc, bis(2,4-pentanedionato-O,O')-, (T-4)-	14024-63-6
50	1H-Benzotriazole, sodium salt	15217-42-2
51	Poly(oxy-1,2-ethanediyl), .alpha.,.alpha.',.alpha.'',=.alpha.'''-[1,4-phenylenebis[methylene(octadecyl=nitrilio)di-2,1-ethanediyl]]tetrakis[.omega.=-hydroxy-, dichloride	68140-77-2
52	Leach solutions, copper, spent	69012-76-6
53	Oils, walnut, polymers with glycerol and phthalic anhydride	68553-87-7
54	Amides, C_{16-18} and C_{18}-unsaturated, N,N-bis (hydroxyethyl)	68603-38-3
55	2-Propenoic acid, 3,3'-(1,4-phenylene)bis-	16323-43-6
56	Lanthanum iodide (LaI_3)	13813-22-4
57	*2,5-Cyclohexadiene-1,4-dione, dioxime	105-11-3
58	*Cyclohexene, 1-ethenyl-	2622-21-1
59	Ethane, 1,1-dichloro-1,2,2,2-tetrafluoro-	374-07-2
60	Hydroxylamine, sulfate (2:1)	10039-54-0
61	2-Naphthalenecarboxanilide, 3-hydroxy-4-[(4-methoxy-=2-nitrophenyl)azo]-	4154-63-6

Number	Chemical	CAS number
62	Benzene, trichloro-, polymer with 1,4-dichlorobenzene and sodium sulfide (Na_2S)	72276-00-7
63	1,4-Benzenedimethanamine	539-48-0
64	1H-Pyrazole-3-carboxylic acid, 1-(3-aminophenyl)-4-=[[2-methoxy-4-[(3-sulfophenyl)azo]phenyl]azo]-, disodium salt	68227-66-7
65	Hexanoic acid, 2-ethyl-, cobalt(2+) salt	136-52-7
66	Urea, polymer with formaldehyde and 1,3,5,7-tetraaza-tricyclo[3.3.1.$1^{3,7}$]decane, butylated ethylated	69898-36-8
67	2-Propenoic acid, 4-(1-methyl-1-phenylethyl)phenyl ester	54449-74-0
68	2-Butene, 1,4-dibromo-, (E)-	821-06-7
69	Benzene, 1-chloro-4-(methylthio)-2-nitro-	1199-36-6
70	8-Quinolinol, 7-C_{12-16}-alkyl derivatives	68511-63-7
71	Phenol, 2,2'-methylenebis[4-chloro-	97-23-4
72	Ethanesulfonic acid, 2-[cyclohexyl(1-oxotetradecyl)=amino]-, sodium salt	63217-16-3
73	Silicon(1+), tris(2,4-pentanedionato-O,O')-, (OC-6-11)-, hexafluoroantimonate(1-)	67251-37-0
74	3H-Pyrazol-3-imine, 2,4-dihydro-5-methyl-2-phenyl-	6401-97-4
75	Benzaldehyde, 4-ethoxy-3-hydroxy-	2539-53-9
76	Acetic acid, cyclohexyl ester	622-45-7
77	Lignosulfonic acid, aluminum salt	9066-49-3
78	Poly(oxy-1,2-ethanediyl), .alpha.-isotridecyl-.omega.-=hydroxy-	9043-30-5
79	Benzenesulfonic acid, 5-chloro-4-ethyl-2-[(2-hydroxy-1-=naphthalenyl)azo]-, barium salt (2:1)	67801-01-8
80	Ethanol, 2,2'-[1,2-ethanediylbis(oxy)]bis-, diacetate	111-21-7
81	Triacontane	638-68-6
82	Urea, N,N''-(4-methyl-1,3-phenylene)bis[N',N'-dimethyl-	17526-94-2
83	Fatty acids, soya	68308-53-2
84	5H-Tetrazole-5-thione, 1,2-dihydro-1-(4-hydroxyphenyl)-	52431-78-4
85	Benzene, 1-bromo-2-methoxy-	578-57-4
86	Benzonitrile, 2-[[4-[(2-cyanoethyl)ethylamino]phenyl]=azo]-5-nitro-	16889-10-4
87	Benzenemethanaminium, N-ethyl-N-[4-[[4-[ethyl[(3-=sulfophenyl)methyl]amino]phenyl](2-sulfophenyl)methyl-=ene]-2,5-cyclohexadien-1-ylidene]-3-sulfo-, hyd-=roxide, inner salt, disodium salt	3844-45-9

Number	Chemical	CAS number
88	Ethanesulfonic acid, 2-[[4-[3-(4,5-dichloro-2-methylphenyl)-4,5-dihydro-1H-pyrazol-1-yl]phenyl]sulfonyl]-, sodium salt	35441-13-5
89	Hydrocarbons, C_4-unsaturated	68956-54-7
90	3H-Indolium, 2-[2-[4-[(2-cyanoethyl)methylamino]phenyl]ethenyl]-1,3,3-trimethyl-, chloride	51980-70-2
91	Benzenesulfonic acid, 2-[(9,10-dihydro-4-hydroxy-9,10-dioxo-1-anthracenyl)amino]-5-methyl-, monosodium salt	4430-18-6
92	Benzamide, 4-amino-N-(2-ethylhexyl)-, monohydrochloride	63589-08-2
93	Oils, rose	8007-01-0
94	Butanedioic acid, acetyl-, dimethyl ester	10420-33-4
95	Alcohols, C_{10}-iso-, distillation overheads	68526-93-2
96	1,3-Isobenzofurandione, polymer with 2,2'-oxybis[ethanol] and 1,2,3-propanetriol	27026-61-5
97	Oils, avocado	8024-32-6
98	Cyclopropanecarboxylic acid, 2,2-dimethyl-3-(2-methyl-1-propenyl)-, (1R-trans)-	4638-92-0
99	Sulfite liquor, pink	68477-10-1
100	2-Propenoic acid, 2-ethylhexyl ester, polymer with N-(1,1-dimethyl-3-oxobutyl)-2-propenamide	26659-51-8
101	Glycerides, tallow mono- and di-, ethoxylated propoxylated	68783-63-
102	Dibenzo[d,f][1,3,2]dioxaphosphepin, 6,6'-[1,6-hexanediylbis(oxy)]bis[2,4,8,10-tetrakis(1,1-dimethylethyl)-	71519-97-6
103	Oxirane, methyl-, polymer with oxirane, hydrogen phosphate (2:1), dibutyl ether	68855-19-6
104	Oils, Atlas cedarwood, oxidized	68916-06-3
105	Propanenitrile, 3-[[3-(branched tridecyloxy)propyl]amino] derivatives	68511-46-6
106	Glycerides, C_{14-22}-linear mono-	68990-53-4
107	Oils, herring, polymerized, oxidized, bisulfited	68648-37-3
108	Vinyl acetal polymers, butyrals, polymers with vinyl acetate and vinyl alcohol	68648-78-2
109	Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-, ether with 1,2,3-propanetriol dodecanoate	57107-95-6
110	Ethanol, 2-[2-[2-(p-aminophenoxy)ethoxy]ethoxy]-	18790-97-1
111	Propanoic acid, 3-mercapto-, 2-ethyl-2-[(3-mercapto-1-oxopropoxy)methyl]-1,3-propanediyl ester	33007-83-9

Number	Chemical	CAS number
112	Propanamide, N-[3-amino-4-(2-methoxyethoxy)phenyl]-	71230-65-4
113	Ferrate(4-), hexakis(cyano-C)-, iron(3+) sodium (1:1:1), (OC-6-11)-	51041-36-2
114	9,10-Anthracenedione, 1-amino-4-bromo-2-methyl-	81-50-5
115	2-Propenoic acid, 2-methyl-, 2-ethyl-2-[[(2-methyl-1-oxo-2-propenyl)oxy]methyl]-1,3-propanediyl ester, polymer with ethenylbenzene	31630-65-6
116	Ethanone, 1,2-diphenyl-	451-40-1
117	Isocyanic acid, polymethylenepolyphenylene ester, polymer with .alpha.,.alpha.'-[oxybis(butoxyphosphinylidene)]bis[.omega.-hydroxypoly[oxy(methyl-1,2-ethanediyl)]], isocyanate-terminated	68908-76-9
118	1-Hexacosanol, dihydrogen phosphate	64131-15-3
119	Copper, [dihydrogen 4-[[2-hydroxy-5-[(2-hydroxyethyl)sufonyl]phenyl]azo]-5-oxo-1(p-sulfophenyl)-2-pyrazoline-3-carboxylato(2-), mono(hydrogen sulfate) (ester)	30053-43-1
120	Nonanedioic acid, dihexyl ester	109-31-9
121	Urea, polymer with formaldehyde and phenol, methylated	68071-43-2
122	Benzenamine, 2-methyl-, polymer with 1,2-dichloroethane	68016-18-2
123	1,3-Benzenedicarboxylic acid, polymer with 2,2-dimethyl-1,3-propanediol, hexanedioic acid and 1,2-propanediol	61809-81-2
124	Fatty acids, linseed-oil, polymers with bisphenol A and epichlorohydrin	67746-09-2
125	Propanoic acid, 3-(dodecylthio)-	1462-52-8
126	7H-Benz[de]anthracen-7-one, 3,9-dibromo-	81-98-1
127	1,3,5-Triazine-1,3,5(2H,4H,6H)-triethanol, compound with bromine (1:1)	53660-25-6
128	Tall oil, polymer with benzoic acid, pentaerythritol and phthalic anhydride	68458-19-5
129	2-Imidazolinium, 1-(carboxymethyl)-2-heptyl-1-(2-hydroxyethyl)-, hydroxide, sodium salt	13039-35-5
130	2H-1-Benzopyran-2-one, 3,4-dihydro-	119-84-6
131	1H-Indole, 2-methyl-1-octyl-	42951-39-3
132	Hydrazine, (3,4-dimethoxyphenyl)-, hydrochloride	20329-82-2
133	1,3-Naphthalenedisulfonic acid, 4-amino-5-hydroxy-, diazotized, coupled with diazotized 2-amino-4,6-dinitrophenol, diazotized 4-amino-5-hydroxy-2,7-naphthalenedisulfonic acid, diazotized 4-amino-3-methylbenzenesulfonic acid, diazotized 4-nitrobenzenamine and resorcinol, sodium salts	72480-09-2

Number	Chemical	CAS number
134	Benzeneacetaldehyde, .alpha.,4-dimethyl-	99-72-9
135	Amides, mixed castor-oil and lard-oil, N,N'-[ethyl=imino)di-2,1-ethanediyl]bis-, ethyl sulfates	68155-18-0
136	Amides, coco, reaction products with phthalic anhydride	68081-99-2
137	Propanamide, 3,3'-dithiobis[N-methyl-	999-72-4
138	Fatty acids, dehydrated castor-oil, polymers with benzoic acid, pentaerythritol, phthalic anhydride and tung oil	70983-81-2
139	Ethanone, 1-(3,4-dimethylphenyl)-	3637-01-2
140	8-Quinolinamine, 4-phenyl-	3637-01-2
141	Cobalt, tris(2,4-pentanedionato-O,O')-, (OC-6-11)	21679-46-9
142	5-Isobenzofurancarboxylic acid, 1,3-dihydro-1,3-=dioxo-, methyl ester	2902-64-9
143	Octadecanoic acid, iron salt	5136-76-5
144	Phenol, 2,4-bis(2-phenyl-1-propenyl)-	68957-56-2
145	1H-Imidazolediacetic acid, 4,5-dihydro-1-(2-hydroxy=ethyl)-2-nonyl-, disodium salt	69929-09-5
146	1,1'-Biphenyl, 4,4'-diisocyanato-3,3'-dimethyl-	91-97-4
147	1-Propanamine, 3-(C_{16-22}-alkyloxy) derivatives	68130-69-8
148	Fatty acids, tall-oil, polymers with coconut oil, glycerol and phthalic anhydride	68188-68-1
149	2-Propenoic acid, 2-methyl-, butyl ester, polymer with butyl 2-propenoate, ethenylbenzene, 2-hydroxyethyl 2-methyl-2-propenoate, methyl 2-methyl-2-propenoate and 2-propenoic acid	57828-93-0
150	Magnesium, bis(2-hydroxybenzoato-O1,O2)-, (T-4)-	18917-89-0
151	2,6-Octadien-1-ol, 3,7-dimethyl-, benzoate, (E)-	94-48-4
152	Pyridine, 2-ethenyl-	100-69-6
153	Tetradecanediol, 1-acetate hydrogen sulfate, sodium salt	65166-19-0
154	4-Pyridinecarboxamide	1453-82-3
155	Alcohols, C_{7-11}, distillation bottoms	68526-82-9
156	Sorbitan, dioctadecanoate	36521-89-8
157	Sulfuric acid, erbium(3+) salt (3:2)	13478-49-4
158	1,4-Benzenedicarboxylic acid, polymer with 1,2-=ethanediol, formaldehyde, methylphenol and 1,3,5-=tris(2-hydroxyethyl)-1,3,5-triazine-2,4,6(1H,3H,=5H)-trione	2198-72-7
160	Oils, carnation	8021-43-0

Number	Chemical	CAS number
161	Poly(oxy-1,2-ethanediyl), .alpha.-(1-oxooctadecyl)-= .omega.-(phosphonooxy)-	58874-55-8
162	Urea, (hydroxymethyl)-	1000-82-4
163	Benzene, diethenyl-, homopolymer, reaction products with 1,1'-(1,3-butadiyne-1,4-diyl)bis[benzene]	68608-81-1
164	Propanenitrile, 3-[[4-[(2,6-dichloro-4-nitrophenyl)= azo]-3-methylphenyl]ethylamino]-	63467-11-6
165	Lanthanum oxide	1312-81-8
166	Propanedioic acid	141-82-2
167	2-Pyridinamine, 4-phenyl-	60781-83-1
168	Amylase, .alpha.-	9000-90-2
169	1,3-Isobenzofurandione, 5,5'-carbonylbis-	2421-28-5
170	.alpha.-D-Glucopyranoside, .beta.-D-fructofuranosyl, reaction products with diethanolamine, ethylene oxide, propylene oxide and triethanolamine	68908-72-5
171	1,2,3-Propanetriol, monoacetate	26446-35-5
172	9-Octadecenoyl chloride, (Z)-	112-77-6
173	2-Propenoic acid, 2-methyl-, polymer with butyl 2-= propenoate, ethenylbenzene, methyl 2-methyl-2-= propenoate and 1,2-propanediol mono(2-methyl-2-= propenoate)	65405-61-0
174	9,10-Anthracenedione, 1,5-diamino-4,8-dihydroxy-	145-49-3
175	Siloxanes and Silicones, dimethyl, diphenyl, methyl vinyl, vinyl group-terminated	68951-95-1
176	2-Butenoic acid, 2-methyl-, ethyl ester, (E)-	5837-78-5
177	C.I. Direct Brown 112	37279-47-3
178	Butanedioic acid, (tetrapropenyl)-	27859-58-1
179	Benzoic acid, 2-(dimethylamino)-, 2-ethylhexyl ester	68921-84-6
180	Isoxazolium, 2-(1,1-dimethylethyl)-5-methyl-, tetra-= fluoroborate(1-)	62796-26-3
181	Holmium telluride (Ho_2Te_5)	12186-84-4
182	Carboxylic acids, C_{10-18}-neo-	68938-08-9
183	Fatty acids, coco, reaction products with isopropanol= amine	68440-05-1
184	Tetradecanamide, N-[4-chloro-3-[[4,5-dihydro-5-oxo-1-= (2,4,6-trichlorophenyl)-1H-pyrazol-3-yl]amino]phenyl]= -2-[3-(1,1-dimethylethyl)-4-hydroxyphenoxy]-	61354-99-2
185	Tungstic acid, cadmium salt (1:1)	7790-85-4
186	9-Octadecanoic acid, 12-hydroxy-, [R-(Z)]-	151-13-3

Number	Chemical	CAS number
187	Phenol, 4-[[4-(phenylazo)-1-naphthalenyl]azo]-	6253-10-7
188	Carbamimidothioic acid, 2-aminoethyl ester, dihydrobromide	56-10-0
189	2-Propenoic acid, polymer with ethyl 2-propenoate, N-(hydroxymethyl)-2-propenamide, 2-propenamide and 2-propenenitrile	65859-34-9
190	Fatty acids, tall-oil, reaction products with diethylenetriamine and linoleic acid dimer	68334-15-6
191	Rosin, polymer with p-tert-butylphenol, formaldehyde, maleic anhydride, pentaerythritol and tung oil	68410-75-3
192	Sulfonic acids, petroleum, sodium salts	68608-26-4
193	Quaternary ammonium compounds, benzyl-C_{10-16}-= alkyldimethyl, chlorides	68989-00-4
194	1,3-Propanediol, 2-ethyl-2-(hydroxymethyl)-, polymer with .alpha.-hydro-.omega.-hydroxypoly(oxy-1,4-= butanediyl) and 1,1'-methylenebis[isocyanato= benzene]	70851-35-3
195	1-Butanol, 2-nitro-	609-31-4
196	Fatty acids, C_{16-18}, esters with sorbitol	72869-62-6
197	Aluminum magnesium oxide, basic	12040-42-5
198	2-Propenoic acid, 2-methyl-, polymer with 1,3-= butadiene, ethenylbenzene and 2-propenenitrile	25214-09-9
199	Benzeneacetamide, .alpha.-oxo-	7505-92-2
200	Oxiranepropanol, .alpha.-ethenyl-.alpha.,3,3-= trimethyl-, acetate	41610-76-8
201	2-Naphthalenesulfonic acid, sodium salt	532-02-5
202	Chromic acid, zinc salt (1:1)	13530-65-9
203	2,7-Naphthalenedisulfonic acid, 5-[[4-chloro-6-= (methylphenylamino)-1,3,5-triazin-2-yl]amino]-4-= hydroxy-3-[(2-sulfophenyl)azo]-, trisodium salt	70210-20-7
204	2-Naphthalenesulfonic acid, 7,7'-(carbonyldiimino)bis= [3-[(3-aminophenyl)azo]-4-hydroxy-, disodium salt	6420-46-8
205	Formaldehyde, polymer with 2-furanmethanol	25989-02-0
206	2-Naphthalenesulfonic acid, 6-hydroxy-, monopotassium salt	833-66-9
207	Caseins, potassium complexes	68131-54-4
208	Oxirane, methyl-, polymer with oxirane, ether with 2,2-bis(hydroxymethyl)-1,3-propanediol (4:1), polymer with 2,2'-[(1-methylethylidene)bis(4,1-= phenyleneoxymethylene)]bis[oxirane]	71832-65-0

Number	Chemical	CAS number
209	Phosphorodithioic acid, O,O-bis(nonylphenyl) ester	28777-73-3
210	9,10-Anthracenedione, 1-amino-4-hydroxy-2-(3-hydroxy=butoxy)-	3224-15-5
211	Ammonium, benzylbis(2-hydroxyethyl)methyl-, hydroxide	33667-49-1
212	Anthra[1,9-cd]pyrazol-6(2H)-one, 9-chloro-2-[2-=(1-methylethyl)-7-oxo-7H-benz[de]anthracen-3-yl]-	61900-99-0
213	Phthalic anhydride, tetrabromo-, polymer with glycerol and propylene oxide	27553-29-3
214	9,12-Octadecadienoic acid (Z,Z)-, dimer, polymer with 2,2'-[(1-methylethylidene)bis(4,1-phenyleneoxy=methylene)]bis[oxirane] and 2-propenoic acid	70529-01-0
215	Benzene, 1,3-diisocyanato-2-methyl-	91-08-7
216	3-Pyridinecarboxylic acid, butyl ester	6938-06-3
217	Safflower oil, conjugated, polymer with glycerol, methylstyrene, phthalic anhydride, soybean oil and styrene	68515-06-0
218	Hexanedioic acid, mixed decyl and octyl esters	68307-93-7
219	Cholest-5-en-3-ol (3.beta.)-, tetradecanoate	1989-52-2
220	Morpholine, 4,4'-(1,2-ethanediyl)bis-	1723-94-0
221	Propanoic acid, 3-(dodecylthio)-, barium salt	38952-49-7
222	Phosphinic acid, sodium salt	7681-53-0
223	Magnesium, dioctyl-	24219-37-2
224	Azulene, 1,2,3,4,5,6,7,8(or 1,2,3,5,6,7,8,8a)-=octahydro-1,4-dimethyl-7-(1-methylethenyl)-	73003-42-6
225	Fluorine	7782-41-4
226	2,7-Naphthalenedisulfonic acid, 3-hydroxy-4-(1-=naphthalenylazo)-, disodium salt	5858-33-3
227	1,3-Benzenedicarboxylic acid, polymer with 2,5-=furandione, hexanedioic acid, 1,3-isobenzofurandione, 2,2'-oxybis[ethanol] and 1,2-propanediol	68140-88-5
228	Maleic acid, bis(2-ethylhexyl) ester, polymer with ethyl acrylate and vinyl acetate	24938-15-6
229	Methylium, tris[4-(dimethylamino)phenyl]-	14426-25-6
230	Amides, soya, N,N-bis(hydroxyethyl)	68425-47-8
231	Benzoic acid, 4-amino-, 2-(diethylamino)ethyl ester, monohydrochloride	51-05-8
232	Hexene, hydroformylation products, low-boiling	70955-03-2
233	Bicyclo[2.2.1]heptane, 2-methoxy-1,7,7-trimethyl-, exo-	5331-32-8

Number	Chemical	CAS number
234	Acetic acid, hydroxy-, compounds with 4,5-dihydro-1H-imidazole-1-ethanamine 2-nortall-oil alkyl derivatives (2:1)	68389-73-1
235	Benzonitrile, 4-chloro-	623-03-0
236	Poly(oxy-1,2-ethanediyl), .alpha.-(1-oxooctadecyl)-.omega.-[(1-oxooctadecyl)oxy]-	9005-08-7
237	Butanoic acid, 3-methyl-, pentyl ester	25415-62-7
238	Distillates (petroleum), straight-run middle	64741-44-2
239	3-Cyclohexene-1-carboxaldehyde, 3,5,6-trimethyl-	67634-07-5
240	Acetamide, N-[2-[(4,5-dicyano-1-methyl-1H-imidazol-2-yl)azo]-5-[ethyl(phenylmethyl)amino]phenyl]-	65059-82-7
241	2-Propenoic acid, ethyl ester, polymer with ethenyl acetate and 2-ethylhexyl 2-propenoate	30900-72-2
242	2,7-Naphthalenedisulfonic acid, 3-[(4-aminophenyl)azo]-4,5-dihydroxy-	15475-84-0
243	Ethanesulfonic acid, 2-[ethyl[4-[(6-methyl-2-benzothiazolyl)azo]phenyl]amino]-, potassium salt	71673-06-8
244	Formaldehyde, polymer with 4,4'-(1-methylethylidene)bis[phenol], oxirane and 4-(1,1,3,3-tetramethylbutyl)phenol	67785-91-5
245	D-Glucose, 4-O-.beta.-D-galactopyranosyl-	63-42-3
246	Aluminum, tris(1-methylethenyl)-, reaction products with magnesium ethoxide and titanium tetrachloride	68411-53-0
247	Glycine, N-(4-hydroxyphenyl)-	122-87-2
248	Terpineol, sulfurized	68784-80-5
249	Calcium silicide	12013-55-7

III

TOXICITY-TESTING NEEDS: EVALUATION OF TOXICITY DATA ELEMENTS

A major objective of this study is to estimate the amount and type of needed toxicity testing of the chemicals of interest, namely the "select universe" of chemicals to which humans are potentially exposed. The decision to test chemicals will be influenced by their suspected toxicity, their intended use, the quantities used, the number of people potentially exposed, and the degree of exposure during intended use, in the occupational environment, and in the ambient environment. The assessment of suspected toxicity involves the evaluation of toxicity data from human studies, case reports, and laboratory animal studies. The Committee on Characterization of Status of Toxicity Data Elements for a Select Universe of Compounds (commonly called the Committee on Toxicity Data Elements or CTDE) is approaching its objective by:

- Describing the general principles that are necessary to evaluate the potential toxic hazard of a chemical.
- Identifying batteries of tests appropriate for chemicals of different use or exposure categories.
- Identifying guidelines by which to judge the quality of individual studies.
- Using the appropriate results from available tests and the relevant guidelines to estimate the needed toxicity testing of chemicals that constitute a sample of the "select universe," to reflect the needed testing of that universe.

On the basis of extrapolation of the needed testing of the sample of chemicals to the needed testing of the "select universe," the NTP will be able to determine more clearly where testing is lacking and may be needed.

During its first year of activity, the Committee established a procedure for decisions and bases for determining the adequacy of toxicity data elements. In its second year, the Committee will examine information on the sample of 100 chemicals and describe the adequacy of the information. During its third year, the Committee will use the results of its investigation of information on the sample to make inferences about the needed testing of the "select universe." This task will be conducted in cooperation with the Committee on Statistical Sampling Methods (commonly called the Committee on Sampling Strategies), which developed the sampling procedure, so that statistical power and variances of statistical estimators can be applied to the inferences about the "select universe."

This chapter contains the results of the CTDE's first year's efforts. An overall strategy for the decision approach to the review and evaluation of information was developed. The general principles necessary for evaluating the potential toxic hazard of a chemical were considered, and batteries of tests were identified as appropriate for different use or exposure categories of chemicals. The guidelines for judging the adequacy of the quality of the tests were described in terms of "currently accepted" reference protocols, where appropriate, and in terms of more basic scientific criteria when judging the quality and adequacy of the results of toxicity tests. These general principles and guidelines will be used to characterize the adequacy of testing of the chemical sample in the second year, during which the reference protocols and batteries of needed tests may be modified as warranted by experience and the appearance of new information.

DECISION APPROACH FOR REVIEW AND EVALUATION OF TOXICITY DATA ELEMENTS

An ideal data base on toxicity of a chemical would contain enough information to identify all its adverse human health effects and to permit the assessment of risks and safety associated with anticipated use and other exposure. Toxicity information obtained from the experience of exposed humans usually is not available, and it is common practice to use information obtained from tests on laboratory animals. Deficiencies in the ideal toxicity data base on a chemical do not invalidate the use of the information to predict at least some human health effects, but may reduce the certainty of a risk estimate for that chemical.

The answers to three fundamental questions describe the adequacy of the toxicity data base on a chemical:

- What toxicity tests on the chemical are needed?
- Is there enough information to assess the human health hazard of the chemical?
- Does the quality of the information permit a health-hazard assessment that is acceptable?

Although the three questions are fundamental to the overall procedure for evaluating the adequacy of a data base, several additional questions of a more detailed or specific nature may be asked as each chemical is examined:

- Is there at least minimal toxicity information on the chemical?
- Is there exposure information on the chemical?
- Have all the tests identified as necessary by the CTDE been conducted?
- Has each of the toxicity tests reported been conducted in a manner conforming to reference protocols?
- If necessary tests have been conducted, but not by reference protocols, did their conduct meet basic criteria of scientific methods?

o If the data from specific tests do not conform to reference protocols, but otherwise meet basic criteria of scientific methods, are they adequate for the assessment of health hazards?

o If the data from specific tests conform to reference protocols, are there other factors that make judgment inappropriate for the assessment of health hazards?

o What is the documentation for a conclusion as to whether available data are sufficient for risk analysis or more tests are required?

The Committee has developed a procedure for determining the adequacy of available toxicity information on a chemical (see Figure III-1). First, a chemical from the "select universe" must be chosen on the basis of the availability of minimal toxicity data, as described in Chapter II. The next step involves a search for pertinent information, as listed in Table III-1, followed by the determination of the major intended use consistent with the category of the "select universe" from which the chemical was selected. Tests needed for each of three exposure settings are then identified: an intended use, an occupational setting, and an ambient environment, as determined from the tables in Appendixes III-2 through III-6. The next step is an estimation of the quality of each test conducted as prescribed in the reference protocols (as listed in Appendix III-7). In selecting the reference protocols for judging the quality of individual studies, the Committee used various resource documents on short-term and long-term toxicity testing, with emphasis on those constructed through international collaborative efforts. The Committee will also consider tests that used procedures that did not meet the specifics of the reference protocols, if their protocols met basic scientific criteria (as described below) and are considered adequate for use in the assessment of a chemical's health hazard. Where the Committee considers the data from toxicity tests to be inadequate, it will document the inadequacy and suggest further testing. A detailed example of the decision approach as applied to a hypothetical chemical is presented later.

The Committee recognizes that the list of protocols may be debatable, and it is presented as the reference for the Committee evaluations; later review by the Committee may indicate the advisability of modifying this reference list, and, if so, the data base may be readily re-evaluated with such modification. Although similarities may be expected, the list is not intended to reflect the attitudes of regulatory agencies.

GENERAL PRINCIPLES FOR EVALUATING TOXIC HAZARDS

In developing general principles for evaluating the toxic hazards of chemicals, the Committee reviewed several reports (National Research Council, 1975, 1977a, 1977b, 1980; Ross *et al.*, 1980).

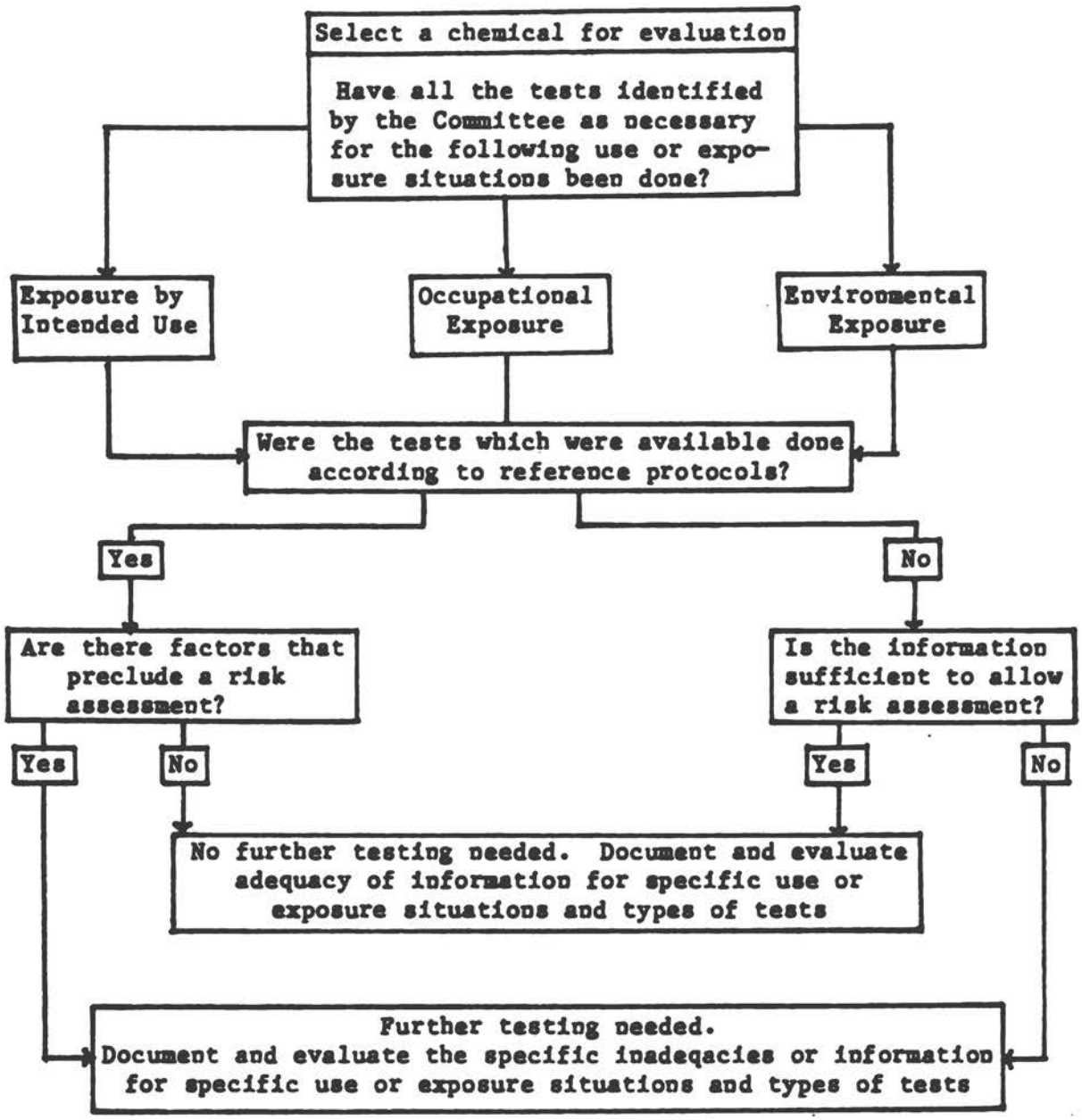

Figure III-1. Outline of a procedure for decision-making when evaluating the adequacy of toxicity information on a specific chemical.

TABLE III-1. Information to be sought in the exhaustive literature search of each chemical in the sample of 100.

Search Category	Information
Chemistry	Synonyms, trade names, structural formula, molecular formula, CAS Registry number, purity, identification and quantity of contaminants, melting and boiling points, specific gravity, vapor pressure, particle size, water solubility, organic solubility, chemical complexity, partition coefficient, pH, dissociation constant, shelf-life, stability, potential for undergoing oxidation and reduction, potential for undergoing hydrolysis under various pH conditions, photolytic reactivity, adsorptivity, and desorptivity
Process	Synthetic pathways (chemical origin, starting materials, stage of appearance in the pathways, final product in the pathways)
Production	Who produces the compound, at what sites, and how much (total volume, volume per site); percent imported, and volume trend (up to 5 yr)
Use	Percent commercial, percent consumer, percent degraded, number and kinds of uses; subcategory: unintentional release during storage, transport, disposal, packaging, manufacture, and industrial use

TABLE III-1(continued). Information to be sought in the exhaustive literature search of each chemical in the sample of 100.

Search Category	Information
Chemical fate	Demographic and geographic distribution, environmental pathway, environmental stability, turnover ($t_{1/2}$), degradation, persistence, partition in soil, water, and air, bioaccumulation, environmental transport, environmental bioavailability
Human exposure	Routes, form, mode (occupational, consumer, etc.), number exposed, frequency of exposure, extent of contact (each episode, total), dose and duration of dose (each episode, total), human rate of absorption
Toxicity	Summary of all available toxicity information (see Appendixes III-1 to III-7)

Conventionally, studies in laboratory animals are intended to identify toxicity (and its severity), for prediction of human risks. The armamentarium of the toxicologist consists of general tests (acute, subchronic, and chronic) that can elucidate adverse effects in many target organs and specialized tests (e.g., for genetic, reproductive-teratologic, neurologic, and behavioral toxicity) that can identify structural and functional changes in substantial detail (National Research Council, 1977a). These tests can be designed to enhance reliability in predicting human risks by selecting appropriate dosages, dosage regimens, routes of administration, and animal models.

The selection of a toxicity test or battery of tests of a substance depends principally on two types of information: the physical-chemical characteristics of the substance and the type and extent of known or anticipated human exposure to it.

Physical-chemical information is useful in selecting and designing toxicity tests. For example, the structure of a molecule may suggest its relative reactivity with biologic structures and imply the likelihood of some adverse effects, such as genetic toxicity; may suggest activation or inactivation of the material in the human body; or may raise suspicions about rates of absorption and excretion that could modify toxicity. The vapor pressure of a substance may indicate the likelihood of inhalation exposure. The octanol-water partition coefficient may indicate potential bioaccumulation and chronic toxicity. For the substances in the 100-member sample, the Committee intends to review the physical-chemical information and use it to draw conclusions on an ad hoc basis about its relevance to toxicity information (see Table III-1).

Exposure is viewed as a function of route and duration. To facilitate the extrapolation of test data to humans, the design of toxicity studies should reasonably approximate conditions of human exposure (National Research Council, 1975, 1977a). A general principle in toxicity testing is the correspondence in route of exposure of laboratory and human populations. Thus, if exposure of humans is via the skin (as in the case of a cosmetic) or via ingestion (as in the case of a food additive), the route of exposure of laboratory animals should be dermal or oral, respectively. However, the Committee recognizes that data from other routes of exposure may also provide information on the toxic potential of a substance.

Reliable exposure data are usually unavailable, so it is often assumed that population risk is directly proportional to the number of people potentially exposed and to the total amount of the material produced. However, these relatively accessible measures can both be misleading. The number of people exposed to a substance is sometimes defined as the number of employees working in a building or at a plant site where the substance is produced or consumed or the number of people downwind of a stack that discharges it. Such populations may include people heavily exposed, but generally also include many who are exposed slightly or not at all. Furthermore, when the total population in question includes groups from different plants or regions, the heterogeneity of exposure within the total population

tends to be magnified; thus, it can be extremely difficult to assign a valid average exposure for a population or any distribution function for the individual exposures.

In the context of route of exposure as a determinant for the selection of toxicity data, the Committee recognizes three exposure situations that would affect the type of potential risk and hence the spectrum of data appropriate to evaluate the risk: exposure via intended use, occupational exposure, and ambient environmental exposure. For example, humans are intentionally exposed to food additives, drugs, and cosmetics. Food additives are meant to be ingested, and cosmetics to be applied to the skin; but drugs are administered in several forms by several appropriate routes. Humans can also be exposed to food additives, drugs, and cosmetics unintentionally during their manufacture and purification; during packaging, transportation, and storage before their intended use; and during disposal of residues and wastes. In the case of most pesticides and TSCA chemicals, there are few intentional exposures of people, but exposures do occur during production, distribution, use, and disposal. The terms "environmental exposure" and "general environmental exposure" (as listed in Appendixes III-2 through III-6) are used to include all potential human exposures other than those related to the workplace or those inherent in the intended use.

The tests that the Committee selected to support risk assessments for substances in various classes of use are listed in Appendixes III-1 through III-6. Batteries of tests are identified for direct and indirect food additives (including colors), drugs (oral, parenteral, dermal, inhalation, ophthalmic, vaginal-rectal, over-the-counter, and veterinary), pesticides, cosmetics, and other marketable chemicals. To the extent feasible, the Committee has selected tests whose routes of exposure are similar to those of humans under varied circumstances.

The Committee recognizes that duration of exposure, as well as route, is intrinsically important in the manifestation and intensity of toxicity in test species and in the prediction of human risk. It has therefore incorporated duration of exposure--acute, subchronic, and chronic--into its selection of toxicity tests for predicting risk (Appendixes III-1 through III-6). For example, if a substance is believed to be present consistently in common foods and lifetime exposure of humans is highly likely, data from chronic-feeding studies are determined as most appropriate for assessing the risk of chronic human intoxication associated with the substance. Similarly, if a substance becomes part of the environment of women of child-bearing age, laboratory studies that investigate possible reproductive injury are considered appropriate for assessing risks in humans.

The Committee also recognizes that exposures often include mixtures of chemicals, rather than single chemical entities. Mixtures of chemicals have the potential for synergistic interactions that may potentiate or antagonize the toxic effects of individual components. Scientific judgment will be required to determine when special studies to evaluate toxic interactions are necessary for adequate evaluation of health hazards in humans.

The evaluation of toxicity data bases to predict human risks must be approached with caution and flexibility. In general, data from properly conducted animal studies are most often predictive of the degree of risk to humans; however, for individual substances, such laboratory investigations may be misleading with regard to target organ, potency, or type of effect. The expert judgment of the Committee will be an essential part of the analysis to ensure the proper use of all available data. For example, the metabolism of a toxicant may be sufficiently different between test species and humans to produce false-negative or false-positive results with regard to possible human risks. The appropriate test battery in itself may be incomplete, but there may be enough other data--such as extensive information on the mechanisms of action in several species--to obviate additional tests. And data from human studies, both epidemiologic and clinical, may be essential in deciding whether to conduct a test on a substance merely for the purpose of completing the recommended battery of tests for that substance. For example, there may already have been human studies of sufficient breadth and sensitivity to obviate toxicity studies in laboratory animals; or clinical studies may have detected skin sensitization or toxicity, so similar investigations in laboratory models would be unnecessary. To the extent feasible, the Committee will analyze data available from human experience (including case studies and retrospective and prospective epidemiologic studies) to delineate the need for further testing.

GUIDELINES FOR ASSESSING THE QUALITY OF INDIVIDUAL TOXICITY STUDIES

The task of assessing the quality of individual toxicity tests addresses the question: Does the quality of the information permit a health-hazard assessment that is acceptable? The first step in the qualitative evaluation of toxicity data on a given chemical will be the determination of compliance with the reference protocols (see Appendix III-7).

The data bases that fall short of the reference protocols will be compiled and judged to see whether the minimal requirements established by the Committee are met. The available data base on a given chemical may be judged sufficient, even if minimal test requirements have not been met.

The Committee anticipates that few chemicals will meet all the requirements of the reference protocols. Because the chemicals in the sample were selected by virtue of the existence of minimal toxicity information on them, there should be very few selected chemicals on which there is no useful information for the assessment of toxicity. Thus, in the case of most of the chemicals, there will probably be some toxicity information missing or some data derived from specifications other than those prescribed in the protocols. Application of the information obtained by comparison of available tests with reference protocols, combined with the judgment of the Committee relative to the basic criteria for scientific methods, will

enable the categorization of chemicals with respect to adequacy of the quality of toxicity data. Chemicals that have most of the toxicity data base completed and on which the information is of adequate quality for predictive purposes would be distinguished from those on which the number and quality of tests are minimal.

SELECTION OF REFERENCE PROTOCOLS

Recent years have seen an effort to develop unified protocols for toxicity studies used to evaluate potential human health hazards of chemicals. The Committee has identified the contribution of the Organisation for Economic Co-operation and Development (1979, 1981), of the Interagency Regulatory Liaison Group (1981a, 1981b, 1981c, 1981d, 1981e), and of the National Research Council (1977a) as the most successful in this regard (see Appendix III-7). With the recognition that rigid protocols are impractical, the reference protocols compile descriptions of standard test methods with sufficient detail to provide the Committee with a basis for sound study design while permitting flexibility where scientific judgment is advantageous. It is recognized that the reference protocols listed in Appendix III-7 may be altered in the future as scientific review proceeds. The Committee will use the most current state-of-the-art documents or will make changes based on its own judgment, but in every case will describe or refer to what was used, so that other scientists can assess the basis of evaluation. The Committee will use the reference protocols as a basis for evaluating the adequacy of specific tests. It should be understood that it was not the Committee's intent to endorse any particular test protocol. Rather, on a pragmatic basis, particular tests were selected as appropriate for judging the adequacy of testing of chemicals. For some situations, the Committee has modified specific tests and identified additional tests. The Committee believes that these modifications and additions will be useful in the development of a data base for risk extrapolation. Whenever this was done, a published document that describes the test system is cited in Appendix III-7.

For behavioral and immunotoxicologic studies, and for broad neurotoxicologic evaluation, widely accepted protocols are lacking. Thus, the Committee has collected publications on these subjects and will develop its own protocols, to be presented in a later report.

In addition to using data from laboratory studies for risk extrapolation, the Committee will give attention to any information on the extent of exposure to a chemical, as well as to epidemiologic studies. The results of animal experiments may provide guidance for planning epidemiologic investigation; but, more importantly, animal data can be most valuable when the epidemiologic evidence is weak, nonspecific, or relatively insensitive. Conversely, good epidemiologic data minimize the need for animal data.

BASIC CRITERIA OF SCIENTIFIC METHODS

The Committee believes that it is impossible to judge the adequacy of past and future studies solely by matching them against protocols that are considered acceptable today. Although strict adherence to rigid protocols tends to ensure adequacy, scientific judgment will be more appropriate in some situations.

The Committee suggests that a study be considered adequate if it meets the following basic critera:

- All elements of exposure are clearly described, including characteristics of the substance purity and stability and the dose, route, and duration of administration.
- Test subjects are predictive of human responses and sensitive to the effects of the material. In toxicity tests of a chemical involving several species, data obtained with the most sensitive species are often used for making risk estimates. This is a conservative approach. When metabolic activation is necessary to produce toxicity and there is evidence that the metabolic pathway in the most sensitive species is different from that in man or the target species, a species with metabolic pathways similar to those of man will probably be chosen.
- Controls are comparable with the test subjects in all respects except the treatment variable. Depending on the study, appropriate controls may be positive, negative, or historical. Historical controls, however, rarely meet this criterion.
- End points answer the specific question addressed in the study and are sufficient to establish a dose-response relationship that can be used in estimating the risk to the target species.
- Analysis and interpretation of results attempt to minimize error. Statistical error, including false positives and false negatives, should be avoided by the use of an appropriate degree of significance and adequate sample size.

The available data on a given chemical may be considered adequate in quality if tests have been performed according to these basic scientific criteria. In addition, several factors, although not critical in deciding whether a given test is adequate, are highly desirable and should be taken into account in any scientific document:

- Subjective elements in scoring should be minimized; quantitative grading of an effect should be used whenever possible. Sometimes, this is not feasible, as when pathologists attempt to judge the extent of malignancy. Such evaluations depend on the experience and training of the pathologists.
- Peer review of scientific papers and of reports is desirable and increases confidence in the adequacy of the work.
- Reported results increase credibility if they are supported by findings in other investigations.
- Similarity of results to results of tests of structurally related compounds increases credibility.
- Evidence of adherence to good laboratory practices improves confidence in the results.

APPLICATION OF THE DECISION PROCEDURE FOR THE EVALUATION OF A SELECTED CHEMICAL

This section presents a hypothetical example of the application of the procedure outlined in Figure III-1 for the stepwise analysis of an available data base on a selected chemical.

- A chemical is selected, on the basis of criteria described in Chapter II by the Committee on Sampling Strategies; for purposes of this example, it is taken to be a direct food additive.
- By reference to Appendix III-2, the tests for the intended use of a direct food additive and for occupational and environmental exposure conditions are identified.
- A summary table (See Table III-2) is initiated by listing all the necessary tests; where applicable, the symbol "NR" (test not required) or "*" (if indicated by available data or information) will be noted in the specific use or exposure column; all remaining blank spaces indicate that the test is necessary and will be filled with the symbols "+" (test performed) or "-" (test not performed); chemistry tests are excluded here for simplification of this hypothetical example.
- A search for information is conducted as described previously, and the symbol "+" or "-" is noted for the necessary tests in Table III-2.
- All other tests not required, but from which information is available on this direct food additive, are listed in Table III-2.
- The dossier of information on this direct food additive is to be provided to the Committee in a combined tabular and descriptive format (see the next section).
- For this hypothetical situation, Table III-2 shows that the answer to the question, "Have all the necessary tests been done?" is "yes" for the intended use, but "no" for occupational and environmental conditions.
- For the intended use of the direct food additive, it is considered (hypothetically) that the results of the 90-d nonrodent subchronic oral-toxicity study (test 12) did not indicate the need for a 6- to 12-mo nonrodent subchronic oral-toxicity study [test 13, labeled *(-)] and that observation in all the other studies did not indicate the need for a 90-d subchronic neurotoxicity study [test 18, *(-)].
- For occupational and environmental exposure, it is considered that a major inadequacy (hypothetical) is the lack of data on inhalation toxicity [test 11, labeled *(-)]; a 90-d oral-toxicity study in rodents is not considered necessary, in view of the availability of a chronic-toxicity study in rats.
- The quality of each test performed (regardless of the "yes" or "no" answer above) is evaluated on the basis of the reference protocols described in Appendix III-7.

Table III-2. Summary of tests for a hypothetical chemical.

Necessary tests (Chemistry tests not included)	Intended use	Occupational exposure	Environmental exposure
1. Acute oral toxicity--rodent	+	+	+
3. Acute dermal toxicity	NR(+)	+	+
5. Acute inhalation toxicity	NR(-)	-	-
6. Acute dermal irritation-corrosivity	NR(+)	+	+
7. Acute eye irritation-corrosivity	NR(+)	+	+
8. Skin sensitization--guinea pig	NR(+)	+	+
9. Subchronic oral toxicity--rodent: 14- or 28-d study	NR(+)	+	+
11. Subchronic oral toxicity--rodent: 90-d study	NR(-)	*(-)	*(-)
12. Subchronic oral toxicity--nonrodent: 90-d study	+	+	*(+)
13. Subchronic oral toxicity--nonrodent: 6- to 12-mo study	*(-)	(-)	*(-)
15. Subchronic dermal toxicity: 90-d study	NR(+)	+	*(+)
16. Subchronic toxicity: 14- or 28-d study	NR(-)	*(-)	*(-)
17. Subchronic inhalation toxicity: 90-d study	NR(-)	-	*(-)
18. Subchronic neurotoxicity: 90-d study	*(-)	NR(-)	NR(-)
19. Teratology study--rodent, rabbit	+	+	+
20. Multigeneration reproduction study--rodent	+	+	(+)
21. Toxicokinetics	*(+)	*(+)	*(+)
22. Carcinogenicity--rodent (mouse)	+	+	(+)
23. Chronic toxicity	NR(+)	+	*(+)
24. Combined chronic toxicity-carcinogenicity--rodent (rat)	+	NR(+)	NR(+)
25. Genetic toxicity	+	+	+
Other tests--not required			
2. Acute oral toxicity--nonrodent	+	+	+
32. Human sensitization studies	+	+	+

° Direct food additive (see Appendix III-2)
NR = Test not required
* = If indicated by available data or information; it will be the responsiblity of the reviewing toxicologist to examine the data from the list of necessary tests and then to make a judgment as to whether these additional tests will also be necessary
+ = Test required and performed
- = Test required and not performed
() = Symbols in parentheses show the findings for tests not required (i.e., tests without checkmark (✓) in Appendix III-2 for the specific use or exposure situation

- For each test performed, a decision is made as to whether the procedures of the reference protocols have been met; if not, the important deficiencies will be listed.
- In the case of test 19, for teratogenic effects in rats, it is observed (hypothetically) that the reference protocol was not followed, in that 15, rather than 20, pregnant animals were used in each test group; thus, test 19 gets a "no" answer. All other tests receive a "yes" answer (hypothetically) to the question on accordance with reference protocols.
- The basis for accepting results that were developed by procedures different from the accepted guidelines in the list of necessary tests will be carefully summarized for later collation with similar information on other chemicals.
- Each test is now examined for accordance with basic criteria for scientific methods for possible influence on the latter yes-no answers above.
- It is found (hypothetically) that all tests meet basic criteria for scientific methods; furthermore, it is considered (hypothetically) that, in view of negative results in teratogenicity studies in rabbits, the relatively large number of pups in the rat study, and the lack of equivocal teratogenic findings in rats, the data are nevertheless sufficient to allow adequate evaluation of the test results; there were no supporting data (hypothetically) from epidemiologic studies of human exposure.
- There are no other factors (hypothetically) that prohibit an evaluation of the adequacy of tests for the intended use of the direct food additive; however, the lack of inhalation-toxicity studies does prohibit an adequate evaluation of occupational and ambient environmental exposures.
- Thus, for the intended use, no further testing is needed (hypothetically); documentation for this decision will include the reasons for considering further nonrodent oral-toxicity or subchronic-neurotoxicity studies unnecessary and for judging the teratology studies to be adequate.
- Further testing is needed (hypothetically) to include the toxic hazard of this direct food additive during manufacture or on release to the ambient environment; documentation will include the need for inhalation studies and the reasons for considering that a 90-d oral-toxicity study in rodents and a 6- to 12-mo subchronic oral-toxicity study in nonrodents are not necessary.
- All the information will be summarized in a document that will serve as the basis for estimating the amount and type of toxicity testing needed for the "select universe."

STRUCTURE OF THE DATA BASE

The test results reviewed in the preceding sections will be used by the Committee to determine whether the toxicity information available on the sample of 100 chemicals is adequate to predict their public health hazard. Because the sample is representative of the

five major categories in the larger "select universe" of chemicals, inferences can be drawn from the sample about the adequacy of toxicity information on chemicals in the "select universe" as a whole.

Such adequacy determinations require that the available toxicity data and related information be acquired and appraised. On the basis of estimates obtained during the procedure to obtain the sample of 100 chemicals, each with minimal toxicity information, it is expected that most of the chemicals will each have fewer than 25 documents describing their toxicity. However, a few compounds may have several hundred documents, and there must be a system for their identification, acquisition, integration, and presentation. A plan has been developed to perform these functions in stepwise fashion, so as to construct an information profile on each of the 100 chemicals in the sample.

SCOPE OF THE LITERATURE

The 100 data files must be as nearly complete as possible if the adequacy of the toxicity information on each compound is to be accurately assessed. The completeness of the collection process is contingent on a search for the data that is as exhaustive as practically possible. Therefore, although virtually all toxicity information for the 100 chemicals will be collected, information of six other kinds is also important in understanding the behavior and exposure potential of these chemicals: chemistry, processing information, production, use, chemical fate, and exposure.

The seven kinds of information (the above six and toxicity information) are interrrelated in the information profile of a chemical. Each of the first six can provide clues for predicting the potential toxic hazard of a chemical from inception, through intentional and unintentional pathways, to degradation. The seventh provides toxicity information that, with the first six, will enable the Committee on Toxicity Data Elements to determine the adequacy of the literature base for predicting the public health hazard of the chemical. Although these seven collectively form all the elements of an exhaustive data profile, only limited information for each of the first six will be sought. Only information pertinent to the predictablity of exposure and public health hazard will be pursued. In the case of toxicity, all information on the tests (e.g., acute oral) and details of the methods used will be vigorously pursued. The data that resulted from the reviewed studies will be available and used as necessary.

The items to be sought in each of the seven categories of information are listed in Table III-1.

PLAN FOR DATA ACQUISITION AND MANIPULATION

Sources of information that will be used include computer data and literature collections, manufacturers and users, originators of the chemical lists from which the sample was drawn, the Toxicology Information Center of the National Research Council, and other, miscellaneous sources.

The computer search will be divided into two phases: (1) a scanning of nine literature and data bases for all 100 chemicals in the sample and (2) a scanning of three or four specialty literature and data bases for the 60 pesticides, cosmetic ingredients, drugs, and food additives in the sample. Manufacturers, users, and importers will be asked to supply the protocols and results of all toxicity studies they have conducted in the categories specified in Appendixes III-2 through III-6 and, by questionnaire, the information in the first six categories of Table III-1. The limited-access files of the Cosmetic, Toiletry and Fragrance Association, the FDA Bureau of Foods, the FDA Bureau of Drugs, and the EPA Office of Pesticides and Toxic Substances will be scanned for toxicity studies on each of the 100 chemicals; only the type of study and details of the methods used will be noted. The National Research Council's Toxicology Information Center and other nonspecific sources will play a supportive role in literature and data acquisition, providing a means for manual searching where necessary, as well as information that was developed before the date of coverage of the computer literature and data collections. The nonspecific sources will be those indicated to be of value by the originators the chemical lists.

The in-house organizational framework that will be used to assimilate, condense, and present the acquired information is identified as seven kinds of information. The components of each are shown in Table III-1. Collectively, this information will form the basis of a dossier on each of the 100 chemicals, to be used by the Committee on Toxicity Data Elements in evaluating the adequacy of the toxicity data base for predicting public health hazard. The seven kinds of information will be maintained in the construction of the dossier and will be presented in a combined tabular and descriptive format.

SUMMARY AND CONCLUSIONS

In preparation for the evaluation of needed testing of chemicals in the human environment, the Committee developed general concepts and procedures that would guide its members in the evaluation of data on toxicity of chemicals in humans and surrogate species and data on known or anticipated exposure to these substances. The approach uses two sequential stages, each of which contains general operating principles and some specific elements of experimental design and data interpretation, which are supplemented with professional judgment to deal with aspects of data analysis that cannot be codified.

The first stage describes the battery of toxicity data elements (e.g., acute-oral, subchronic-inhalation, or oral-carcinogenesis) that should be available to judge the relative risk of a substance under conditions of its intended use, of its manufacture, and of its environmental dissemination and modification. The Committee identified 33 types of toxicity data and several categories of chemical information from which various batteries of tests would be selected for each substance.

The second stage addresses the evaluation of the quality of individual studies to determine the extent to which their results might be suitable for predicting risks to human health from exposure to a substance. The Committee has relied on current designs for toxicity studies and epidemiologic investigations to serve as references for its evaluation.

Having completed the generation of concepts and procedures for the evaluation of data, the Committee will apply them to the information on the 100 chemicals in the sample of the "select universe." For each chemical, data deficiencies will be described, if present, on the basis of the characteristics described for both stages of the evaluation. It is intended that the Committee's findings will provide a basis on which the magnitude of NTP testing needs may be projected.

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APPENDIX III-1

Tests for evaluating the potential health hazards of chemicals--according to identified uses.[1]

Appendix III-2: Testing under varying situations of chemical use and general exposure to direct and indirect food additives.

Appendix III-3: Testing under varying situations of chemical use and general exposure to an oral or parenteral drug or a color additive for sutures.

Appendix III-4: Testing under varying situations of chemical use and general exposure to dermal, inhalation, and ophthalmic drugs.

Appendix III-5: Testing under varying situations of chemical use and general exposure to vaginal-rectal, over-the-counter, and veterinary drugs.

Appendix III-6: Testing under varying situations of chemical use and general exposure to pesticides, cosmetics, and other marketable chemicals.

Symbols and reference notations

✓ = Appropriate test; the list of checked tests will be considered as the minimal necessary tests for the evaluation of an adequate data base

* = If indicated by available data or information; it will be the responsibility of the reviewing toxicologist to examine the data from the list of necessary tests and then to make a judgment as to whether these additional tests also will be necessary

(a) = Use another rodent other than rat

(b) = Use rat only

(c) = Do this test if carcinogenicity is suspected

(d) = Lifetime - rat for nonabsorbable sutures
Short-term - for absorbable sutures
Ocular - for ophthalmic sutures

(e) = Do repeat patch test with photosensitization test

(f) = Acute toxicity should be determined in 3 to 4 species by appropriate route(s) of intended use

(g) = By appropriate route of intended use

(h) = Will also require up to 6-month study by appropriate route

(i) = 18- or 24-month study

(j) = 12-month study

(k) = May require up to 6 months on intact skin

(l) = 4 species: 3 hours/day (5 days/week) under conditions to be used clinically

(m) = 1 species: duration commensurate with clinical use

(n) = 2 species: local toxicity by appropriate use

(o) = Duration and number of applications determined by intended use

(p) = Additional studies appropriate to duration and route of intended use: some studies required in target species; if target species is a food-producing animal, see direct food additive in Appendix III-2
(q) = Or perform test #24
(r) = Or perform tests #22 and #2

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1 The Committee recognizes that the list of protocols may be debatable, and it is presented as the reference for the Committee evaluations; later review by the Committee may indicate the advisability of modifying this reference list, and, if so, the data base may be readily re-evaluated with such modification. Although similarities may be expected, the list is not intended to reflect the attitudes of regulatory agencies.

Appendix III-2

Testing under varying situations of chemical use and general exposure to direct and indirect food additives.

Data and tests	Direct food additives (including colors)	Indirect food additive			General exposure	
		Virtually nil migration < 0.05 ppm	Insignificant migration 0.05 ppm to 1 ppm	Significant migration ≥ 1 ppm	Occupational	Environmental
Chemistry						
Identification data	✓	✓	✓	✓	✓	✓
Production and disposal data					✓	✓
Physical data	✓	✓	✓	✓	✓	✓
Reactivity data					✓	✓
Methods data						✓
Bioavailability data						✓
Toxicology						
1. Acute oral toxicity--rodent	✓	✓	✓	✓	✓	✓
2. Acute oral toxicity--nonrodent		*				
3. Acute dermal toxicity					✓	✓
4. Acute parenteral toxicity						
5. Acute inhalation toxicity					✓	✓
6. Acute dermal irritation-corrosivity					✓	✓
7. Acute eye irritation-corrosivity					✓	✓
8. Skin sensitization--guinea pig					✓	✓
9. Subchronic oral toxicity--rodent: 14- or 28-d study		✓			✓	✓
10. Subchronic toxicity--nonrodent: 14- or 28-d study						

Appendix III-2 (continued)

Testing under varying situations of chemical use and general exposure to direct and indirect food additives.

Data and tests	Direct food additives (including colors)	Indirect food additive			General exposure	
		Virtually nil migration < 0.05 ppm	Insignificant migration 0.05 ppm to 1 ppm	Significant migration ≥ 1 ppm	Occupational	Environmental
11. Subchronic oral toxicity--rodent: 90-d study			✓		*	*
12. Subchronic oral toxicity--nonrodent: 90-d study	✓		✓	✓	*	*
13. Subchronic oral toxicity--nonrodent: 6- to 12-mo study	*			*	✓	*
14. Subchronic dermal toxicity: 21- or 28-d study						
15. Subchronic dermal toxicity: 90-d study					✓	*
16. Subchronic inhalation toxicity: 28- or 14-d study					*	*
17. Subchronic inhalation toxicity: 90-d study					✓	*
18. Subchronic neurotoxicity: 90-d study	*					
19. Teratology study--rodent, rabbit	✓		✓	✓	✓	✓
20. Multigeneration reproduction study--rodent	✓		*		✓	*
21. Toxicokinetics	*			*	*	*
22. Carcinogenicity--rodent	✓[a]	*[c]	*[c]	✓[a]	✓	*
23. Chronic toxicity					✓	*
24. Combined chronic toxicity-carcinogenicity--rodent	✓[b]			✓[b]		

Appendix III-2 (concluded)

Testing under varying situations of chemical use and general exposure to direct and indirect food additives.

Data and tests	Direct food additives (including colors)	Indirect food additive			General exposure	
		Virtually nil migration < 0.05 ppm	Insignificant migration 0.05 ppm to 1 ppm	Significant migration ≥ 1 ppm	Occupational	Environmental
25. Genetic toxicity	✓	✓	✓	✓	✓	✓
26. Subchronic eye toxicity						
27. Segment I: Fertility and reproductive performance						
28. Segment III: Perinatal and postnatal						
29. Acute delayed neurotoxicity						
30. Skin painting--chronic						
31. Implantation studies						
32. Human sensitization studies						
33. Skin penetration studies						

Appendix III-3

Testing under varying situations of chemical use and general exposure to an oral or parenteral drug or a color additive for sutures.

Data and tests	Period of Oral or Parenteral Use				Color additive for sutures	General exposure	
	Several days	Up to 2 weeks	Up to 3 months	6 months to unlimited		Occupational	Environmental
Chemistry							
Identification data	✓	✓	✓	✓	✓	✓	✓
Production and disposal data						✓	✓
Physical data	✓	✓	✓	✓	✓	✓	✓
Reactivity data						✓	✓
Methods data							✓
Bioavailability data							✓
Toxicology							
1. Acute oral toxicity--rodent	✓[f]	✓[f]	✓[f]	✓[f]		✓	✓
2. Acute oral toxicity--nonrodent	✓[f]	✓[f]	✓[f]	✓[f]			
3. Acute dermal toxicity						✓	✓
4. Acute parenteral toxicity	✓[f]	✓[f]	✓[f]	✓[f]			
5. Acute inhalation toxicity						✓	✓
6. Acute dermal irritation-corrosivity						✓	✓
7. Acute eye irritation-corrosivity						✓	✓
8. Skin sensitization--guinea pig						✓	✓
9. Subchronic oral toxicity--rodent: 14- or 28-d study	✓[g]	*[g]	*[g]			✓	✓
10. Subchronic toxicity--nonrodent: 14- or 28-d study	✓	*[g]	*[g]				

Appendix III-3 (continued)

Testing under varying situations of chemical use and general exposure to an oral or parenteral drug or a color additive for sutures.

Data and tests	Period of Oral or Parenteral Use				Color additive for sutures	General exposure	
	Several days	Up to 2 weeks	Up to 3 months	6 months to unlimited		Occupational	Environmental
11. Subchronic oral toxicity--rodent: 90-d study		✓[g]	✓[h]	*[g]		*	*
12. Subchronic oral toxicity--nonrodent: 90-d study		✓[g]	✓[h]	*[g]		*	*
13. Subchronic oral toxicity--nonrodent: 6- to 12-mo study				✓[j]		✓	*
14. Subchronic dermal toxicity: 21- or 28-d study							
15. Subchronic dermal toxicity: 90-d study						✓	*
16. Subchronic inhalation toxicity: 28- or 14-d study						*	*
17. Subchronic inhalation toxicity: 90-d study						✓	*
18. Subchronic neurotoxicity: 90-d study			*	*			
19. Teratology study--rodent, rabbit	✓	✓	✓	✓		✓	✓
20. Multigeneration reproduction study--rodent	✓	✓	✓	✓		✓	*
21. Toxicokinetics	*	*	*	*		*	*
22. Carcinogenicity--rodent				*	*[c]	✓	*
23. Chronic toxicity				✓[i]		✓	*
24. Combined chronic toxicity-carcinogenicity--rodent				*			

Appendix III-3 (concluded)

Testing under varying situations of chemical use and general exposure to an oral or parenteral drug or a color additive for sutures.

Data and tests	Period of Oral or Parenteral Use				Color additive for sutures	General exposure	
	Several days	Up to 2 weeks	Up to 3 months	6 months to unlimited		Occupational	Environmental
25. Genetic toxicity	✓	✓	✓	✓		✓	✓
26. Subchronic eye toxicity							
27. Segment I: Fertility and reproductive performance	✓	✓	✓	✓			
28. Segment III: Perinatal and postnatal	✓	✓	✓	✓			
29. Acute delayed neurotoxicity	*	*					
30. Skin painting--chronic							
31. Implantation studies					✓[d]		
32. Human sensitization studies							
33. Skin penetration studies							

Appendix III-4

Testing under varying situations of chemical use and general exposure to dermal, inhalation, and ophthalmic drugs.

Data and tests	Dermal drug	Inhalation (general anesthetics)	Ophthalmic drug	General exposure	
				Occupational	Environmental
Chemistry					
Identification data	✓	✓	✓	✓	✓
Production and disposal data				✓	✓
Physical data	✓	✓	✓	✓	✓
Reactivity data				✓	✓
Methods data					✓
Bioavailability data					✓
Toxicology					
1. Acute oral toxicity--rodent			*[f]	✓	✓
2. Acute oral toxicity--nonrodent			*[f]		
3. Acute dermal toxicity	✓			✓	✓
4. Acute parenteral toxicity		*			
5. Acute inhalation toxicity				✓	✓
6. Acute dermal irritation-corrosivity	✓			✓	✓
7. Acute eye irritation-corrosivity				✓	✓
8. Skin sensitization--guinea pig	✓			✓	✓
9. Subchronic oral toxicity--rodent: 14- or 28-d study				✓	✓
10. Subchronic toxicity--nonrodent: 14- or 28-d study					

Appendix III-4 (continued)

Testing under varying situations of chemical use and general exposure to dermal, inhalation, and ophthalmic drugs.

Data and tests	Dermal drug	Inhalation (general anesthetics)	Ophthalmic drug	General exposure	
				Occupational	Environmental
11. Subchronic oral toxicity--rodent: 90-d study				*	*
12. Subchronic oral toxicity--nonrodent: 90-d study				*	*
13. Subchronic oral toxicity--nonrodent: 6- to 12-mo study				✓	*
14. Subchronic dermal toxicity: 90-d study	✓				
15. Subchronic dermal toxicity: 90-d study	✓[k]			✓	*
16. Subchronic inhalation toxicity: 28- or 14-d study		✓[1]		*	*
17. Subchronic inhalation toxicity: 90-d study				✓	*
18. Subchronic neurotoxicity: 90-d study					
19. Teratology study--rodent, rabbit	✓	✓	✓	✓	✓
20. Multigeneration reproduction study--rodent	✓	✓	✓	✓	*
21. Toxicokinetics	*	*	*	*	*
22. Carcinogenicity--rodent				✓	*
23. Chronic toxicity				✓	*
24. Combined chronic toxicity-carcinogenicity--rodent					

Appendix III-4 (concluded)

Testing under varying situations of chemical use and general exposure to dermal, inhalation, and ophthalmic drugs.

Data and tests	Dermal drug	Inhalation (general anesthetics)	Ophthalmic drug	General exposure	
				Occupational	Environmental
25. Genetic toxicity	✓	✓	✓	✓	✓
26. Subchronic eye toxicity			✓[m]		
27. Segment I: Fertility and reproductive performance	✓	✓	✓		
28. Segment III: Perinatal and postnatal	✓	✓	✓		
29. Acute delayed neurotoxicity					
30. Skin painting--chronic	*				
31. Implantation studies					
32. Human sensitization studies	*				
33. Skin penetration studies					

Appendix III-5

Testing under varying situations of chemical use and general exposure to vaginal-rectal, over-the-counter, and veterinary drugs.

Data and tests	Vaginal-rectal drug	Over-the-counter drug	Veterinary drug	General exposure: Occupational	General exposure: Environmental
Chemistry					
Identification data	✓	✓	✓	✓	✓
Production and disposal data				✓	✓
Physical data	✓	✓	✓	✓	✓
Reactivity data				✓	✓
Methods data					✓
Bioavailability data					✓
Toxicology					
1. Acute oral toxicity--rodent	*[f]	✓[f]	✓[p]	✓	✓
2. Acute oral toxicity--nonrodent	*[f]	✓[f]	✓[p]		
3. Acute dermal toxicity		✓[f]		✓	✓
4. Acute parenteral toxicity		✓[f]			
5. Acute inhalation toxicity		✓[f]		✓	✓
6. Acute dermal irritation-corrosivity	✓[h]	*[f]		✓	✓
7. Acute eye irritation-corrosivity		*[f]		✓	✓
8. Skin sensitization--guinea pig		*[f]		✓	✓
9. Subchronic oral toxicity--rodent: 14- or 28-d study				✓	✓
10. Subchronic toxicity--nonrodent: 14- or 28-d study					

Appendix III-5 (continued)

Testing under varying situations of chemical use and general exposure to vaginal-rectal, over-the-counter, and veterinary drugs.

Data and tests	Vaginal-rectal drug	Over-the-counter drug	Veterinary drug	General exposure: Occupational	General exposure: Environmental
11. Subchronic oral toxicity--rodent: 90-d study	✓[o]	*	✓[p]	*	*
12. Subchronic oral toxicity--nonrodent: 90-d study	✓[o]		✓[p]	*	*
13. Subchronic oral toxicity--nonrodent: 6- to 12-mo study				✓	*
14. Subchronic dermal toxicity: 21- or 28-d study					
15. Subchronic dermal toxicity: 90-d study		*		✓	*
16. Subchronic inhalation toxicity: 28- or 14-d study		*		*	*
17. Subchronic inhalation toxicity: 90-d study		*		✓	*
18. Subchronic neurotoxicity: 90-d study					
19. Teratology study--rodent, rabbit	✓	✓		✓	✓
20. Multigeneration reproduction study--rodent	✓	✓		✓	*
21. Toxicokinetics	*	*		*	*
22. Carcinogenicity--rodent		*[i]		✓	*
23. Chronic toxicity		✓		✓	*
24. Combined chronic toxicity-carcinogenicity--rodent		*			

Appendix III-5 (concluded)

Testing under varying situations of chemical use and general exposure to vaginal-rectal, over-the-counter, and veterinary drugs.

Data and tests	Vaginal-rectal drug	Over-the-counter drug	Veterinary drug	General exposure	
				Occupational	Environmental
25. Genetic toxicity	✓	✓		✓	✓
26. Subchronic eye toxicity					
27. Segment I: Fertility and reproductive performance	✓	✓			
28. Segment III: Perinatal and postnatal	✓	✓			
29. Acute delayed neurotoxicity					
30. Skin painting--chronic					
31. Implantation studies					
32. Human sensitization studies					
33. Skin penetration studies					

Appendix III-6

Testing under varying situations of chemical use and general exposure to pesticides, cosmetics, and other marketable chemicals.

Data and tests	Pesticide	Cosmetic for topical use (incl. color additive)		Other marketable chemicals	General exposure	
		Skin only	Skin and eye area		Occupational	Environmental
Chemistry						
Identification data	✓	✓	✓	✓	✓	✓
Production, disposal data					✓	✓
Physical data	✓	✓	✓	✓	✓	✓
Reactivity data					✓	✓
Methods data						✓
Bioavailability data						✓
Toxicology						
1. Acute oral toxicity--rodent	✓			✓	✓	✓
2. Acute oral toxicity--nonrodent						
3. Acute dermal toxicity	✓	✓	✓	✓	✓	✓
4. Acute parenteral toxicity						
5. Acute inhalation toxicity	✓			✓	✓	✓
6. Acute dermal irritation-corrosivity		✓		✓	✓	✓
7. Acute eye irritation-corrosivity	✓	*	✓	✓	✓	✓
8. Skin sensitization--guinea pig	✓	✓	✓	✓	✓	✓
9. Subchronic oral toxicity--rodent: 14- or 28-d study				✓	✓	✓
10. Subchronic toxicity--nonrodent: 14- or 28-d study						

Appendix III-6 (continued)

Testing under varying situations of chemical use and general exposure to pesticides, cosmetics, and other marketable chemicals.

Data and tests	Pesticide	Cosmetic for topical use (incl. color additive)		Other marketable chemicals	General exposure	
		Skin only	Skin and eye area		Occupational	Environmental
11. Subchronic oral toxicity--rodent: 90-d study	✓			✓	*	*
12. Subchronic oral toxicity--nonrodent: 90-d study	✓			✓	*	*
13. Subchronic oral toxicity--nonrodent: 6- to 12-mo study					✓	*
14. Subchronic dermal toxicity: 21- or 28-d study	✓	✓	✓	✓		
15. Subchronic dermal toxicity: 90-d study		*	*		✓	*
16. Subchronic inhalation toxicity: 28- or 14-d study	✓				*	*
17. Subchronic inhalation toxicity: 90-d study					✓	*
18. Subchronic neurotoxicity: 90-d study	*			✓		
19. Teratology study--rodent, rabbit	✓			✓	✓	✓
20. Multigeneration reproduction study--rodent	✓			✓	✓	*
21. Toxicokinetics	✓			✓	*	*
22. Carcinogenicity--rodent	✓[q]	*[c]	*[c]	✓	✓	*
23. Chronic toxicity	✓[q]			✓	✓	*
24. Combined chronic toxicity-carcinogenicity--rodent	✓[r]					

Appendix III-6 (concluded)

Testing under varying situations of chemical use and general exposure to pesticides, cosmetics, and other marketable chemicals.

Data and tests	Pesti-cide	Cosmetic for topical use (incl. color additive)		Other marketable chemicals	General exposure	
		Skin only	Skin and eye area		Occupa-tional	Environ-mental
25. Genetic toxicity	✓	✓	✓	✓	✓	✓
26. Subchronic eye toxicity			✓			
27. Segment I: Fertility and reproductive performance						
28. Segment III: Perinatal and postnatal						
29. Acute delayed neurotoxicity	*					
30. Skin painting--chronic		✓	✓			
31. Implantation studies						
32. Human sensitization studies		✓[e]	✓[e]			
33. Skin penetration studies		*	*			

Appendix III-7

Reference protocols for toxicity testing.

Test	Reference sources
1. Acute oral toxicity--rodent	IRLG,[a] 1981c
2. Acute oral toxicity--nonrodent	OECD,[b] 1981, pp. 401:1-7;[c] when using a rabbit as a nonrodent, fewer than 10 (5 per sex) at each dose level will be acceptable; for dogs or other large nonrodents, an ascending-dose study will be acceptable
3. Acute dermal toxicity	IRLG, 1981a
4. Acute parenteral toxicity	OECD, 1981, pp. 401:1-7; guidelines for acute oral toxicity should be followed, but administration will be by intravenous, intramuscular, subcutaneous, or intraperitoneal routes
5. Acute inhalation toxicity	NRC,[d] 1977a
6. Acute dermal irritation-corrosivity	OECD, 1981, pp. 404:1-6
7. Acute eye irritation-corrosivity	IRLG, 1981b
8. Skin sensitization--guinea pig	OECD, 1981, pp. 406:1-9; see addition to paragraph 3.2 (Interpretation of Results) attached
9. Subchronic oral toxicity--rodent: 14- or 28-d study	OECD, 1981, pp. 407:1-9
10. Subchronic toxicity--nonrodent: 14- or 28-d study	OECD, 1981, pp. 407:1-9
11. Subchronic oral toxicity--rodent: 90-d study	OECD, 1981, pp. 408:1-10
12. Subchronic oral toxicity--nonrodent: 90-d study	OECD, 1981, pp. 409:1-9
13. Subchronic oral toxicity--nonrodent: 6- to 12-mo study	OECD, 1981, pp. 409:1-9
14. Subchronic dermal toxicity: 21- or 28-d study	OECD, 1981, pp. 410:1-1
15. Subchronic dermal toxicity: 90-d study	OECD, 1981, pp. 411:1-10

[a] Interagency Regulatory Liaison Group
[b] Organisation for Economic Co-operation and Development
[c] Penultimate version of OECD guidelines
[d] National Research Council

Appendix III-7 (continued)

Test	Reference sources
16. Subchronic inhalation toxicity: 28- or 14-d study	NRC, 1977a
17. Subchronic inhalation toxicity 90-d study	NRC, 1977a
18. Subchronic neurotoxicity: 90-d study	OECD, 1979, pp 106-109
19. Teratology study--rodent, rabbit	IRGL, 1981d
20. Multigeneration reproduction study--rodent	U.S. Environmental Protection Agency, 1978
21. Toxicokinetics	OECD, 1981, pp. 415:1-15
22. Carcinogenicity--rodent	OECD, 1981, pp. 451:1-19
23. Chronic toxicity	OECD, 1981, pp. 452:1-15
24. Combined chronic toxicity-carcinogenicity-rodent	OECD, 1981, pp. 453:1-16
25. Genetic toxicity	OECD, 1979, pp. 114-116
26. Subchronic eye toxicity	U.S. Department of Health, Education, and Welfare, 1973[e]
27. Segment 1: fertility and reproductive performance	U.S. Department of Health, Education, and Welfare, 1973[e]
28. Segment III: perinatal and postnatal performance	U.S. Department of Health, Education, and Welfare, 1973[e]
29. Acute delayed neurotoxicity	U.S. Environmental Protection Agency, 1978.
30. Skin painting--chronic	OECD, 1981, pp. 451:1-15
31. Implantation studies	Guidelines for chronic oral toxicity (number 23) should be followed with test material implanted, rather than administered in diet or parenterally
32. Human sensitization studies	Marzulli and Maibach, 1980
33. Skin penetration studies	Marzulli et al., 1969

[a] Interagecy Regulatory Liaison Group
[b] Organisation for Economic Co-operation and Development
[c] Penultimate version of OECD Guidelines
[d] National Research Council
[e] Further descriptions of segments I and III, the Food and Drug Administration Bureau of Drugs' requirements for reproduction studies, may be found in Collins (1978)

IV

SETTING PRIORITIES FOR TOXICITY TESTING

The number of chemicals to be assessed by the NTP for potential hazard to public health far exceeds present testing capabilities. Hence, it is necessary to select for study in depth only substances that appear most deserving of investigation.

A number of selection criteria have been advanced. These include the toxicity of the substances in question, the number of people exposed, the severity of their exposure, the persistence and possible accumulation of the substances in the food chain, and socioeconomic and political considerations. To the extent that relevant information is lacking, incomplete, uncertain, or expensive to compile, various compromises in the priority-setting process are unavoidable.

This chapter, the report of the Committee on Priority Mechanisms, reviews the major priority-setting efforts of federal and state agencies, private institutions, and international organizations. Although the series of systems reviewed in this report (Appendix IV-2) does not include all efforts to categorize substances with respect to relative potential public-health impact, it reflects a wide spectrum of approaches.

The literature on priority-setting systems is growing rapidly, but few full descriptions of procedures have been published. Some of those surveyed here are to be found in unpublished contractor reports, some have appeared in the Federal Register, and some are under development and not officially available. As a result, the Committee's survey of priority-setting procedures has been supplemented by inquiries to individuals and organizations known or thought to be concerned with such procedures.

To facilitate its review, the Committee has addressed some aspects of its task through subgroups: one on toxicity information, one on exposure information, and one on overall methodology and integration. Surveys by each subgroup of the state of the art in its subject have been crucial to the Committee's evaluation of the priority-setting systems reviewed here. They have also guided preliminary attempts to formulate a priority-setting system to meet the needs of the NTP.

It seemed indisputable that any effort to develop a priority-setting system should begin with a survey of existing systems; however, review of existing systems and decisions concerning the relevance of their elements to the NTP program require some evaluation criteria. But establishing criteria before a review risks missing some important elements, selecting inappropriate elements, and otherwise failing to maximize the benefits of the survey.

To circumvent this problem, the Committee first assembled the existing systems easily identified. These were then scanned to determine their elements, their objectives, the processes they used, and the universes of chemicals they were designed to rank. On the basis of this rather small series of priority-setting systems, the Committee began to reflect on the NTP's universe of chemicals and to ask, of the existing systems, which elements appear appropriate for the NTP. As a result, the

Committee's discussions moved repeatedly between the particulars of existing systems and attempts at generalizations concerning the formulation of a system consistent with the specific mandate, programs, and needs of the NTP.

This iterative process has both increased the Committee's appreciation of the difficulties in its assignment and helped to prepare it for designing a system to meet the needs of the NTP. Additional iterations are likely to lead to further evolution in the Committee's perspective on the problem, so these comments are intended to stress the tentative nature of this report, which describes only the preparatory stages of a larger undertaking.

Although the review of priority-setting systems presented here is largely descriptive, with analytic treatment by the Committee to follow during the next phase of its work, several observations deserve comment. First, few of the existing systems deal adequately with a problem of major importance to the NTP--namely, the extent to which lack or uncertainty of information is a constraint in the selection and ranking of substances for testing. Second, few of the systems give adequate recognition to the need for developing a strategy for testing that enables the different types of necessary information to be obtained in the most cost-effective order. Third, few systems adequately define the role of expert judgment, as opposed to numerical scoring, in the priority-setting process. Fourth, in evaluating the capabilities of existing systems in relation to the needs of the NTP, one must distinguish criteria that are appropriate in selecting substances for testing from those which are appropriate in selecting substances for regulatory action. These and other problems are mentioned in this chapter.

SCOPE OF MAJOR REPORTED PRIORITY-SETTING EFFORTS

Federal agencies have taken the lead in the development of priority-setting schemes, although state governments, international agencies, and private concerns have shown an interest. Much of the relevant literature is in the form of draft reports and other internal documents; little has made its way into the conventional literature.

Three compilations of priority-setting schemes were available. A report to the Office of Technology Assessment includes 32 lists of chemicals; six lists resulted from priority-setting schemes (Kornreich et al., 1979). Eighteen priority-setting schemes were reviewed for their applicability to the needs of the Environmental Protection Agency (Ross and Lu, 1980). The literature on priority-setting schemes for toxic chemicals was reviewed in an unpublished doctoral dissertation (Wilhelm, 1981).

FEDERAL ACTIVITIES

Office of Technology Assessment

The Office of Technology Assessment (OTA) has published Environmental Contaminants in Food (Congress of the United States, 1979), which included, as an appendix, excerpts from a report by Clement Associates, Inc., Priority Setting of Toxic Substances for Guiding Monitoring Programs (Kornreich et al., 1979).

The latter reviewed 32 lists of chemicals, compiled over the preceding 5 yr, mostly by or for government agencies concerned with monitoring, testing, or regulation. Only six of the lists presented the chemicals in order of priority. The lists were examined for the methods and criteria that were used to generate them, and a set of criteria was developed by which chemicals could be ranked on the basis of their likelihood of endangering human health through contamination of the food supply.

Environmental Protection Agency: Interagency Testing Committee

The Interagency Testing Committee (ITC) was created by Section 4 of the Toxic Substances Control Act (TSCA) to advise the Administrator of the EPA as to the chemicals already in commerce that should undergo testing for health and environmental effects. Chemicals recommended by the ITC for testing by their manufacturers cannot exceed 50 at any given time. The ITC is required by TSCA to update the list of designated chemicals every 6 mo. In the eight reports it has submitted to the EPA since 1977, the ITC has designated a total of 46 chemicals or classes for testing. Chemicals are removed from the list when the EPA issues testing rules for them or publishes its reasons for not doing so.

Although TSCA stipulates that the ITC shall rank the chemicals that it recommends for testing, the ITC has chosen not to do so, on the grounds that all designated chemicals are to be of equal priority for testing. The ITC has, however, developed a priority-setting process by which chemicals are initially scored by experts for exposure potential. High-scoring chemicals are then scored for health-effects potential, and the chemicals scoring highest at that stage are scrutinized individually for final selection (Nisbet, 1979; Rosen, 1981).

In early 1979, the ITC convened a workshop to review its scoring procedure regarding various aspects of exposure and toxicity evaluation. Workshop participants recommended some elaboration and modification of the ITC's scoring procedures, but did not challenge the basic approach of the ITC scoring system (Enviro Control, 1979).

In addition to a description of the development of the ITC scoring system and detailed analysis of each of its components, the proceedings of the scoring workshop included descriptions of several scoring systems and of innovative approaches to scoring.

A modified scoring system for environmental effects was developed by a followup workshop (Ross and Welch, 1981).

Environmental Protection Agency: Assessment Division, Office of Pesticides and Toxic Substances

The Assessment Division, Office of Pesticides and Toxic Substances (OPTS), is responsible for preparing the EPA's responses to testing recommendations from the ITC, as well as for other evaluative activities concerning environmental chemicals. In response to its own needs to identify chemicals that have a high probability of requiring review for regulation or testing, the Assessment Division has taken initiatives to develop its own scoring procedures for priority-setting.

The Oak Ridge National Laboratory has undertaken for the Assessment Division a study on chemical scoring system development. The study includes a survey and evaluation of existing scoring systems and the development of a system for use by the Assessment Division. The new system scores chemicals in five ways: production and release, human exposure, two categories of biologic toxicity, and environmental fate. Scoring occurs in two stages; the chemicals receiving the highest scores for exposure are considered first for scoring for biologic toxicity (Ross and Lu, 1980).

The EPA has published an annotated bibliography of chemical selection methods for use in priority-setting, ranking, indexing, and sorting (Gervetz et al., 1980).

An OPTS staff member familiar with the problem of establishing testing priorities under TSCA has developed a priority scheme in a doctoral dissertation. This scheme is designed to use machine-accessible data to calculate 17 scores per chemical. These scores are to be used by an expert panel in setting priorities for testing (Wilhelm, 1981).

Food and Drug Administration

The Food and Drug Administration (FDA) is developing a unified approach to the safety evaluation of food additives through a cyclic review process, elements of which have been published over the last few years (Food Chemical News, 1979, 1980). The plan draws on several earlier approaches for setting priorities for food-additive testing, such as the recommendations of the Food Safety Council (1980).

Occupational Safety and Health Administration

The Occupational Safety and Health Administration (OSHA) has published a list of substances that, on the basis of brief scientific review, are considered candidates for further scientific review and possible identification, classification, and regulation as potential occupational carcinogens (U. S. Department of Labor, 1980a). Although OSHA did not include either an explicit system for setting priorities or a method for screening and classifying the large number of substances reported or alleged to be carcinogenic, it stated that omission of an explicit priority system did not mean that it was oblivious to the

importance of setting priorities. OSHA noted that, although it had received many comments and suggestions on methods of setting priorities, the comments received were not particularly helpful for developing a specific priority-setting system (U. S. Department of Labor, 1980b, p. 5208). The agency announced its intention to devise a screening and priority-setting system that would be flexible and use available data efficiently.

National Cancer Institute

The Drug Development Program of the National Cancer Institute (NCI) has a procedure for the application of structure-activity relationships to the selection of candidate molecules for evaluation in its cancer chemotherapy program (National Cancer Institute, 1976).

With support from NCI, the Stanford Research Institute has developed procedures for ranking compounds for possible carcinogenic hazard. One procedure applies structure-activity relationships to predict carcinogenesis. A group of experts follow a decision tree to estimate the probability of a chemical's being carcinogenic (Dehn and Helmes, 1974). A second procedure calculates a hazard index from exposure and probability of carcinogenicity. Exposure to a chemical is estimated for each route of exposure (Gori, 1977).

National Science Foundation

In an early effort at priority-setting for testing of chemicals, the National Science Foundation (NSF) in 1974 assembled a group of 10 scientists to identify compounds that might be of present or future interest with respect to environmental or health effects. Data on production, use, disposal, properties, and toxicity were reviewed. After application of specific screening criteria, expert judgment was used in the final ordering process (Stephenson, 1977).

The National Toxicology Program

The Annual Plan for FY 1980 describes the NTP's methods to select chemicals for testing (U. S. Department of Health, Education, and Welfare, 1979). The NTP operates on the principle that industry will test chemicals for health and environmental effects as intended and mandated by the Congress under legislative authorities. However, some chemicals will not likely be tested by the private sector, and the NTP selects chemicals for its own testing program from the following categories:

- Chemicals found in the environment that are not closely associated with commercial activities.

- Desirable substitutes for existing chemicals, particularly therapeutic agents, that might not be developed or tested without federal involvement.
- Chemicals that should be tested to improve scientific understanding of structure-activity relationships and thereby assist in defining groups of commercial chemicals that should be tested by industry.
- Some chemicals tested by industry or by others of which additional testing by the federal government is justified to verify the results.
- Previously tested chemicals of which other testing is desirable to compare testing methods.
- Marketed chemicals with potential for significant human exposure that are of social importance, but that generate too little revenue to support an adequate testing program.
- Chemicals that are likely to be members of combinations to which people will be exposed (testing of such combinations probably cannot be required of industry if the products of different companies are involved).
- In special situations, as determined by the NTP Executive Committee, marketed chemicals that have potential for large-scale or intense human exposure, even if it may be possible to require industry to perform the testing.

The NTP solicits lists of chemicals from NTP research agencies (NCI, NIEHS, and NIOSH) and regulatory agencies (FDA, OSHA, CPSC, and EPA), other federal agencies, academia, industry, labor, and the public. All the chemicals suggested for study are funneled to the NTP Chemical Nominations Group.

The Chemical Evaluation Committee (CEC)--which is composed of representatives from EPA, OSHA, FDA, CPSC, NIH, NIEHS, and NTP--prepares a dossier describing what is known about the physical properties of each chemical, its production volume, its use, exposures to it, and toxicity information. Each chemical is judged against the chemical selection principles described above, and nominations are forwarded to the NTP Board of Scientific Counselors for review in a meeting open to the public. The Board's nominations, ranked in priority order, are then transmitted to the NTP Executive Committee, with nominations from the CEC, for final decisions about chemicals to place on tests and tests to perform. A decision by the NTP to test a chemical does not necessarily mean that the chemical will be placed in a bioassay program; it may mean that the chemical will be entered first into less expensive short-term tests whose results will determine the need for more elaborate testing.

STATE ACTIVITIES

State agencies were surveyed to determine what actions they had taken to establish priorities for dealing with hazardous chemicals. Most state agencies respond to initiatives taken by federal programs and do not attempt to establish their own priorities. Michigan, however, has

developed a system to select chemicals for inclusion in a Critical Materials Register of water pollutants (Michigan Department of Natural Resources, 1980). Chemicals are selected on the basis of a system that assigns scores to seven types of biologic activities.

INTERNATIONAL ACTIVITIES

Several intergovernmental organizations conduct programs concerned with some aspect of chemical safety: the World Health Organization (WHO), the International Labor Organization (ILO), the United Nations Environment Program (UNEP), the Organization for Economic Cooperation and Development (OECD), and the Commission of the European Communities. Recently the WHO, UNEP, and ILO jointly launched the International Program for Chemical Safety (IPCS). The International Register for Potentially Toxic Chemicals (IRPTC), serving as the lead institution of the IPCS to collect information in chemicals, has developed a formula for presenting data to evaluate possible hazards from chemicals (United Nations Environment Programme, 1979).

Intergovernmental organizations conducted two efforts to develop lists of chemicals of priority concern for internal purposes. Both efforts used panels of experts to develop lists based on the informed judgment of the experts. A task force was convened by WHO and the Commission of the European Communities to develop a list of priority industrial chemicals for evaluation by the IPCS. The task force decided to develop criteria for including chemicals and then to use the criteria to choose the chemicals by informed judgment. The task force considered a list of chemicals developed by the IPCS Secretariat.

The International Agency for Research on Cancer (IARC) Monographs Program collects published data, analyzes and evaluates these data through international working groups of experts, and publishes the evaluations as IARC monographs. An *ad hoc* panel was convened to reevaluate the criteria for selecting chemicals as topics for future monographs (International Agency for Research on Cancer, 1979). The panel recommended the following criteria: there are published data related to carcinogenicity in humans or experimental systems, and there is evidence of human exposure. Chemicals meeting these criteria are to be given priority based on the extent of human exposure, specific populations that may be at increased risk, the amounts of the chemicals produced, and the findings in short-term screening tests.

The European Economic Community (EEC) contracted with SRI International to develop and apply a priority-setting scheme to rank compounds for regulation or study as possible pollutants of the fresh water of EEC countries. Data on production of a chemical, fraction of production reaching fresh water, river flow, and half-life are used to calculate concentration. The calculated concentrations are combined with toxicity data to produce an index of hazard to human health and aquatic organisms (Brown *et al.*, 1980).

PRIVATE-SECTOR ACTIVITIES

The Flavor and Extract Manufacturers Association developed a scheme that uses structure-activity relationships to place food chemicals into one of three levels of concern. Chemicals in the highest level of concern are to be tested first (Cramer *et al.*, 1978).

The Chemical Manufacturers Association (CMA) has developed a draft framework for setting chemical testing priorities (Chemical Manufacturers Association, 1980). This document presents a rationale for priority-setting and outlines key steps in the process. It does not present details of a scoring system.

The Cosmetic Ingredient Review (CIR) was established to evaluate the safety of ingredients used in cosmetic products. The CIR has developed and published a ranking process of cosmetic ingredients. Ingredients are scored on the basis of seven factors, including frequency of application by particular groups and suggestion of biologic activity (Cosmetic, Toiletry and Fragrance Association, 1978).

The Eastman Kodak Company has developed a system of sequential testing for chemical risk assessment that uses a scoring system to determine what tests are required to evaluate health and environmental hazard. Data from recommended tests are used to reevaluate chemicals for further testing needs (Astill *et al.*, 1981).

Enslein and colleagues have developed statistical models relating toxicologic end points to chemical structure. The structure of the compound is portrayed numerically by molecular connectivity indexes and substructure keys that were used to predict the results of studies on *Salmonella typhimurium* assays (Ames test) (Enslein *et al.*, 1981; Craig and Enslein, 1981).

Litton Bionetics, Inc., has developed a scoring system for processing the results of *in vitro* and submammalian mutagenesis test batteries (Brusick, in press).

A system has been proposed that places suspected carcinogens in one of three categories for possible regulatory action. The categories are known human carcinogenesis, confirmed animal oncogenesis, and substances for further testing (Reinhardt, 1979). Nees (1979a, 1979b) has described the Hooker Chemical Company scoring matrix for oncogenic potential; it is derived from the sum of scores for animal studies, epidemiology studies, and screening tests.

GENERAL FEATURES OF PRIORITY-SETTING SYSTEMS

DEFINITION OF CHEMICAL SUBSTANCES

Testing priorities may be set for pure, well-defined compounds, commercial grades of such compounds, elements and all their compounds, categories of compounds (e.g., cyanides), mixtures of known or unknown composition, radicals, or other classes of chemical entities. We use the terms "substance" and "chemical" interchangeably to include all these classes, even though "chemical" is more properly restricted to elements

or compounds. It is important in designing an exposure assessment, a toxicity assessment, and their interface to define as precisely as possible the substances being considered. The most commonly accepted and usually unambiguous identifier for a substance is its Chemical Abstracts System (CAS) Registry Number. However, priority schemes should also be able to deal with substances that are less well characterized than required by the CAS.

SINGLE-STAGE OR SEQUENTIAL SCREENING

Systems for screening chemicals for priority-setting may be designed in one stage or multiple stages. In one-stage systems, the same screening criteria and procedures are applied to all the chemicals under consideration. In the simplest type of multistage system, chemicals are screened out of the system at each successive stage; the only chemicals considered in the last stage are those which have survived all the earlier stages. A more complex type of multistage system is the decision tree, in which the screening criteria applied at each stage depend on the outcome of the previous stage.

The priority-setting systems reviewed by the Committee included examples of each of these three types of systems. In most multistage systems, the first stage is a simple screen based on chemical class, uses, or production volume; the second stage is based on criteria that reflect exposure; and the third stage and later stages are based on criteria that reflect toxicity or potential risks. Although this sequence is a feature of six different systems, the reasons for its choice were not made explicit; it probably reflects the fact that crude indexes of use, production, and exposure are relatively easy to obtain for large numbers of chemicals, whereas indexes of toxicity are more difficult to acquire and require more scientific review and judgment. In the most elaborate systems--the decision tree of Cramer *et al.* (1978) and the six-stage linear screen described by Nisbet (1979)--the late stages require fairly extensive compilations of toxicity and risk data and fairly detailed scientific review.

The advantages of multistage systems are that the screening criteria can use simple, readily retrieved data, so chemicals of low priority can be eliminated from consideration quickly, focusing most scientific attention on the chemicals of greatest interest. Systems of this kind appear to be the only practical way to deal with very large numbers of chemicals. An offsetting disadvantage, however, is that the criteria used in the early stages are necessarily crude, so that some chemicals may be eliminated erroneously at an early stage. Another disadvantage is that exposure information is usually considered in less detail than toxicity information, so chemicals with unusual pathways of exposure may not be identified. The only practical way to alleviate these problems is to include provision for adding back chemicals eliminated in early stages or to reintroduce consideration of exposure factors in late stages. These features are included in the TSCA-ITC system, but both require the exercise of scientific judgment and hence the expenditure of time by experts.

Decision-tree systems are in principle more flexible than linear multistage systems, because they can use more appropriate criteria for screening at some stages. However, the systems that have been proposed to date require relatively precise information and would be difficult to use for broad classes of chemicals, especially chemicals with little or no toxicity testing.

The design of a multistage screening system involves balancing of the costs of generating information on a large number of chemicals in early stages against the costs of generating more detailed information on fewer chemicals in late stages. The efficiency of such a system depends on the number of stages, the amount of information considered in each stage, and the number of chemicals eliminated at each stage. In the systems reviewed by the Committee, these characteristics appear to have been chosen subjectively, and it is not clear that maximal efficiency was achieved.

NARROWING THE UNIVERSE OF CHEMICALS UNDER STUDY

The first stage in any priority-setting exercise is to establish the universe of substances from which the high-priority chemicals are to be selected. Although the importance of this initial step is rarely explicit, it usually involves some initial screening or the exclusion of some candidate chemicals. Some of the schemes reviewed by the Committee have been applied only to specific classes of chemicals (such as food additives or drugs); others have been applied only to chemicals on existing priority lists or to chemicals nominated by panels of experts. In the latter case, the chemicals have already been screened through a process that involves scientific judgment, so chemicals on which there is little information are very likely to have been excluded without adequate review. Thus, the establishment of the initial universe in itself constitutes a significant and error-prone step in the priority-setting process.

In several of the schemes reviewed by the Committee, the universe is immediately narrowed by the deletion of substances that are judged to be either irrelevant to the exercise or difficult to review. Classes of substances deleted in this way include the following:

- Chemicals already regulated, such as pesticides, drugs, and food additives (whether or not tests of these chemicals have been sufficient).
- Substances not subject to regulation, such as natural products, tobacco, alcoholic beverages, and other drugs of abuse.
- Chemicals nominally subject to regulation, but not adequately tested under existing regulations, such as cosmetic ingredients and GRAS substances.
- Substances without CAS numbers, including complex and ill-defined mixtures.

- Other substances difficult to characterize, including combustion products, pyrolysis products, and environmental breakdown products.
- Environmental mixtures, such as extracts of air pollutants and water pollutants.

Although the omission of such substances and mixtures can usually be understood on the grounds of convenience and practicality, it should be recognized that the classes of substances that are omitted include many that are both poorly characterized and potentially harmful. Thus, the initial steps to narrow the universe of chemicals can be very important steps in the priority-setting process.

EVALUATION OF EXPOSURE POTENTIAL

To produce effects on human health, a substance not only must possess some intrinsic biologic activity, but also must be used or distributed in ways that result in human exposure. Exposure is a concept that, although clear in general terms, has thus far defied precise definition, except in specific applications. Furthermore, even when a definition is precise, information may not be available to measure exposure. Consequently, assessments of exposure have used indexes that serve as approximations of or surrogates for exposure. In increasing order of sophistication, indexes of exposure have been based on production; the gross quantities of chemicals released into the human environment; types of use or dispersion of the chemicals; the concentration of chemicals in air, water, food, and other materials or objects to which humans are exposed; and the doses (quantities) of chemicals taken in by humans over a specified time and by a specified route.

The exposure-assessment component of a priority system is usually designed to characterize one or more of the following: consumer exposures, occupational exposures, community exposures, general environmental exposures, and accidental exposures.

In principle, a priority scheme should describe who is exposed to what substances by what route, over what times, in what setting, and to what extent. In practice, these end-result exposures may be directly measurable, as in the administration of a drug in known dose patterns, but more often they are estimated or inferred from knowledge of the processes that lead from production or liberation of a substance to the final human contact.

Some of the important exposure elements are production and use leading to direct exposure or environmental release; fate in the environment, including persistence, bioaccumulation, and transport; and behavior of the population at risk, including numbers of people in a position to be exposed.

Depending on the degree of discrimination designed into the corresponding toxicity assessment, the exposure assessment may need to specify the routes of entry by which humans are exposed. The principle routes of exposure are oral, dermal, and respiratory.

EVALUATION OF HEALTH EFFECTS

The data for evaluating the potential for human health effects are frequently sparse, incomplete, inadequate, or absent. When adequate data are available, there is no need for priority-setting. When data are inadequate, priority-setting must proceed on the basis of inferences drawn from indirect evidence. The process of establishing the potential of a chemical substance to produce biologic effects involves the consideration of many types of data. The starting point of any evaluation is customarily knowledge of chemical composition, chemical identity, and structure. The type of activity that is expected may be predicted from structure-activity considerations. Precise structure-activity correlations are limited to a few classes of compounds, but with expert opinion and judgment it is increasingly possible to identify potential kinds of biologic activity from knowledge of chemical structure. Additional useful data in this early assessment phase include physicochemical properties, such as physical state, molecular weight, volatility, solubility, and dissociation constants. Chemical stability and reactivity may be taken into account at this point. Recently, a number of *in vitro* or short-term tests have been developed to provide a basis for prediction of biologic activity. These tests are particularly useful with respect to genotoxicity and are valuable adjuncts to the design and interpretation of longer-term animal studies. Human exposure data, when available, are customarily included at this point, such as those derived from case histories and accidental exposures during workplace and consumer use. Limitations on the data available suggest the need to provide for the use of inferential data and distinguish them as such. If schemes also have feedback mechanisms, to accommodate later test results that confirm or deny inferential data, changes in priorities can be made.

The largest source of information on biologic effects is animal experimentation. It is convenient to assess such data in terms of lethality, structural impairment, and functional impairment, with some consideration of the reversibility or irreversibility of impairment. Information of this type is commonly derived from acute, subchronic, or chronic studies. The performance of such studies usually depends on the type and extent of concern raised by exposure information or on suggestive findings in preliminary experimental or epidemiologic studies. Ultimately, the process of evaluating human health effects from studies in animals requires extrapolation. This involves appropriate animal models and routes of exposure, knowledge of mechanisms of action, metabolic and pharmacokinetic studies, and the use of margins of safety or risk-assessment processes. Metabolic and mechanistic information, if available, may also play a part in the early assessment phase.

It is useful to consider the ordering of biologic-effects data sequentially. This sequence corresponds to the level of concern that may be generated for a substance. Such a sequence may proceed through the inferential data discussed above, through acute lethality and *in vitro* tests, to long-term studies directed at one or more toxic end points. Ordering of such data, or the requirement to generate such data, may be a component of priority-setting schemes.

In the initial phases of toxicity assessment, the questions asked are frequently general or speculative. As the priority-setting process becomes more sophisticated, the available data may need careful evaluation, both for inherent validity and reliability and for quality and relevance. Such factors as adequacy of experimental design, dose-effect relationships, correctness of interpretation, and statistical treatment of data may require evaluation before a degree of concern or a testing priority is assigned.

The use of toxicity data in priority-setting exercises usually requires a compromise between breadth and depth. In the later stages of analysis, when only a few candidate chemicals are under review, it may be possible to conduct critical reviews of important toxicity studies. In earlier stages, however, when large numbers of chemicals have to be screened, it is usually necessary to rely on research papers, on abstracts, or even on computerized compilations.

ROLES OF NUMERICAL SCORING AND EXPERT JUDGMENT

When the number of chemicals to be ranked is small, they can be ranked by experts without the use of any elaborate priority-setting criteria or procedures. The number of criteria that must be considered for ranking a given chemical tends to be large, however, so a list of chemicals to be evaluated does not need to be very long for some sort of numerical and mechanical scoring to be essential.

The use of numerical scores and algorithms cannot, in any event, entirely eliminate the need for expert evaluation. Scores must be assigned by experts, and inferences must often be drawn from inadequate data. Structure-activity relationships are being programed for computer analysis, but this process also generally depends on expert judgment. Most systems include sufficient flexibility to allow expert opinion to play a substantial role, no matter how automated some steps in the priority-setting process may be. Flexibility in the application of formulas and algorithms is possible through the provision of "subjective override," which enables chemicals to be raised or lowered in priority by human intervention at any stage in the process.

Virtually all priority-setting systems use some sort of numerical process to provide an initial ranking of the candidate chemicals. Although many qualitative factors may come into play, both before and after the quantitative phase, several quantifying procedures are usually used in ranking the candidates. These include scoring, modeling, sorting, and ordinal ranking:

- In scoring systems, the data elements used as ranking criteria are assigned numerical scores (usually integers), and the scores are combined by a rule (often a weighted addition) to yield a single score that represents relative toxicity, relative exposure, or relative overall concern.
- In contrast, modeling-based systems use the data elements directly (kilograms of chemical produced, LD_{50} in milligrams per

kilogram, etc.) and then combine the data elements into an index that represents the degree of human exposure, the degree of toxicity, or the overall health hazard.

- Sorting (or screening) procedures answer questions regarding aspects of exposure and toxicity and sort chemicals into categories in accordance with the answers. The chemicals in each category are then ranked according to judgments as to which ones represent greater or more important hazards.
- In ordinal ranking, the chemicals are ranked on each of various elements of exposure and toxicity, and the ranks are combined, according to a rule, to derive an overall ranking.

Most systems explicitly include expert judgment. Many include a screening mechanism to select chemicals on which more extensive data are to be gathered. Screening is followed by ranking based on a priority-setting algorithm, a committee of experts, or both.

INTEGRATION OF EXPOSURE AND TOXICITY ASSESSMENTS

The exposure and toxicity assessments should each produce two kinds of information: best estimates of the degree of exposure or toxicity--disaggregated by route of exposure and other factors if necessary--and an evaluation of the reliability of these estimates. The best estimates of exposure and toxicity can be combined to produce a best estimate of the degree of concern warranted.

However, degree of concern alone is not sufficient to set priorities for testing. If a substance is already well tested, the reliability of the toxicity estimate will be high, and there will be little need for further testing.

In the case of a chemical for which the reliability of the exposure assessment is high, but the reliability of the toxicity assessment is low, the data from toxicity testing will contribute greatly to the decision on whether exposure should be reduced. If the reliability in the toxicity estimate is high, there is less chance that a decision will wrongly exonerate a hazardous chemical or wrongly indict a safe one. If the reliability of the exposure assessment is low, then the information from a toxicity test would be less valuable in reaching a decision, unless the uncertainties about exposure were also resolved.

The concept of testing may be expanded to include the gathering of information on exposure. Analysis of reliability can then guide the choice among gathering more exposure information, conducting toxicity tests, or acting without additional information.

Finally, the integrated analysis of toxicity assessments, exposure assessments, and their reliability can be more finely examined to determine which tests are most valuable in reducing uncertainty about societal concern and thereby facilitating control decisions.

OVERVIEW OF CHARACTERICTICS OF REPORTED PRIORITY-SETTING SYSTEMS

PURPOSE

All the schemes surveyed (see Appendix IV-2) begin with lists of chemicals and end with shorter lists. Either implicitly or explicitly, most of the schemes appear to pursue the goal of minimizing harm from chemicals. According to this objective, the "worst" chemicals are selected for testing first. The "worst" chemicals are those on which the available toxicity information is inadequate to indict them conclusively, but adequate to suggest that they pose a substantial hazard to health under prevailing or anticipated conditions of use and exposure.

Several of the schemes rely implicitly on the concept of "value of information"--i.e., the value of information depends on the degree to which it increases the probability that some action will be taken or some decision reached. Thus, the testing of a substance that presents a reasonably well-defined and important risk to health may be of little value if testing is unlikely to increase markedly the probability of action. However, testing of a substance on which there is some suggestive evidence, but little explicit information, might well be of greater value. The value of an increase in information (through testing or other means) must also, of course, be weighed at least qualitatively against the cost of the increase.

Having begun with at least some statement of purpose and principles, most schemes jump to the offered procedure with little explanation of why that procedure was chosen in preference to alternatives, how well it might meet the stated purpose, or how the performance of the procedure could be evaluated or improved with experience.

APPLICABILITY

Different schemes are designed for different chemical groups. There are priority-setting procedures for food additives, food contaminants, industrial and commercial chemicals, water pollutants, and potential carcinogens. Every scheme devotes considerable care to the definition of its own universe and to the implications of the size and nature of that universe. Two factors of particular concern here are the number and heterogeneity of the chemicals in the NTP universe.

STRUCTURE

Of the schemes surveyed, four (Astill *et al.*, 1981; Nisbet, 1979; Kornreich *et al.*, 1979; Ross and Lu, 1980) are in essence scoring procedures, three (Food Chemical News, 1979, 1980; Cramer *et al.*, 1978; Wilhelm, 1981) rely principally on sorting, and three (Brown *et al.*,

1980; Dehn and Helmes, 1974; Gori, 1977) are based on modeling as a fundamental design principle. However, some hybridization among the procedures is apparent. Some of the scoring systems combine all the exposure-element scores into one total-exposure score, whereas others keep the element scores separate (after some aggregation) and leave selection to experts who process the individual scores subjectively. The modeling systems are designed to produce one final exposure-ranking index, even if separated by route of exposure. Where sorting is used, the categories are usually related to different testing needs. In some cases, "testing" needs are defined broadly enough to include the gathering of additional information related to exposure.

CHARACTERIZATION OF EXPOSURE

Only a minority of schemes (Astill et al., 1981; Brown et al., 1980; Cramer et al., 1978; Gori, 1977) define exposure in unambiguous, quantitative, physical terms. For example, scoring systems, although numerically precise in assigning scores, cannot assign physical meaning to the aggregate exposure score. Some schemes define exposure physically in terms of average or aggregate human intake rates. The most commonly used definition is total per capita intake of a chemical over 1 yr, or an equivalent expression. Several of the schemes are not explicit in this regard and leave the reader to work out the units of exposure and the method by which they are estimated. Several do not use physical units of exposure at all (Kornreich et al., 1979; Nisbet, 1979; Ross and Lu, 1980; Wilhelm, 1981), but define the data elements that should be used to estimate exposure, usually through a scoring approach

None of the schemes explicitly matches a potential exposure (for example, ambient air concentrations) to the population at risk (number of people experiencing those concentrations). However, a few include the idea of geographic distribution of exposures by using the number of production facilities, with the thought that such decentralization implies greater potential for human exposure. Several of the schemes mention frequency of exposure as a factor in their design, but the ideas are not well developed with respect to their significance for toxicity assessment (chronic vs acute hazards). One scheme includes a crude separation between acute and chronic exposures.

Although in principle many of the schemes could be made applicable to a wide range of exposure sources, in practice they are strongly oriented to manufactured, or at least processed, chemicals. Very little attention is paid in any of the systems to natural substances other than those mobilized by man (e.g., natural flavors and colors, minerals, and metals). Waste products, chemicals formed in accidents, or the metabolic and degradation products of chemicals are not important design considerations.

Several of the schemes (Astill et al., 1981; Dehn and Helmes, 1974; Gori, 1977; Nisbet, 1979; Ross and Lu, 1980; Wilhelm, 1981) attempt to be fairly broad in the kinds of exposure situations treated (e.g., consumer, occupational, and general environmental exposure). Others are either

explicitly or implicitly slanted toward specific settings, especially exposures via food or drinking water. None of the systems addresses accidental exposures in any serious way.

Depending on objectives, the schemes differ greatly in the detail in which they treat exposure processes. For example, a scheme that deals with direct food additives needs to consider only two basic processes: occurrence in foods and ingestion of those foods. Others are much more elaborate; one system that includes concern for all populations and exposure routes has 22 exposure-related data elements. The most common exposure elements are production and use, followed by the size of population groups that may be exposed.

Several schemes (Brown et al., 1980; Kornreich et al., 1979; Nisbet, 1979; Ross and Lu, 1980) consider some measures of chemical fate, such as persistence and bioaccumulation. Few explicitly consider disposal processes, and none considers other risk factors in the exposed population groups.

A few of the schemes explicitly estimate exposure by route (ingestion, inhalation, or percutaneous absorption), and others rank exposure as high if it can occur through more than one route. Several schemes, by virtue of their concentration on one exposure situation, imply only one route of exposure. A few do not discriminate at all by route of exposure.

CHARACTERIZATION OF TOXICITY

The various schemes characterize toxicity by using one or more of the following types of toxicity data: lethality, reversible impairment, irreversible impairment, and predictive data. Predictive data are physicochemical measurements and results of toxicity tests performed on biologic systems other than intact mammals. In about half the schemes, only lethality data (generally acute LD_{50}s) are used. Reversible impairment or functional effects, usually not specifically identified, are considered in some of the schemes. But most of the schemes take into consideration at least some aspect of irreversible impairment. Most schemes also use predictive data in their assessment of toxicity.

When data on irreversible impairment are used, there is usually a weighting in favor of effects that have high public concern--carcinogenesis, mutagenesis, and teratogenesis or other reproductive impairments. Very little specific attention is given to other forms of impairment, such as irreversible neuronal degeneration or such reversible changes as altered lung function or inhibition or induction of enzymes.

Some of the schemes are concerned primarily with carcinogenesis or carcinogenic potential and thus do not address a full range of toxic responses. In only two of the schemes do the scoring criteria use the lack of toxicity data (Kornreich et al., 1979; Nisbet, 1979). One of these uses a two-phase scoring system that consists of a measure of known toxicity and a measure of the need for additional data (Nisbet, 1979).

There is no uniformity with respect to whether compounds are scored on the basis of dose-response relationships or strictly on a dichotomous (positive-negative) basis. There is a tendency to treat genotoxicity-related effects (carcinogenesis and mutagenesis) on a dichotomous basis. Scoring in these cases is generally related to the nature of the test used to elicit the effect (e.g., positive results of whole-animal bioassays are given higher scores in many systems than positive results of related short-term or in vitro assays).

Several schemes attempt to reflect the degree of a toxic effect. One scheme scores for the frequency with which an effect has been reported (Wilhelm, 1981). Where acute toxicity is scored, the scores reflect the degree of toxicity by being inversely related to the LD_{50}. In some cases where chronic or subchronic effects are scored, the score is adjusted according to dose-response data.

In most cases, there is a scale of scores for one or more toxic effects. In a few cases, the effects are weighted or a multiplying factor is applied to scores for health effects of greatest concern.

Ranking is sometimes accomplished by a series of steps, reducing large groups of compounds to smaller groups on the basis of a screening plan. In other cases, several different effects of a chemical are scored on an equivalent scale and added to arrive at an overall ranking. The ranking systems usually tend to give high scores to compounds on which data demonstrate one or more adverse effects. In some systems, a single high score for any one of a group of effects under consideration would cause a chemical to be given a high priority rating.

Only one or two schemes attempt to develop means for ranking suspicion of injury potential independently from the ranking for demonstrated adverse effects. The latter is a very important consideration when setting priorities for regulation, which would depend heavily on existing data. No scheme seemed entirely adequate for scoring degree of concern in the absence of definitive data, and this criterion is the key to setting priorities for testing. Some schemes produce a summary score for the priority-setting process, but are organized to display individual scores as well.

The use of expert judgment is seldom explicitly discussed in the descriptions of the schemes, although toxicity data require interpretation. Interpretative elements include dose-response relationships, quality of data, and experimental design. Generally, expert judgment is also required to define classes of chemicals according to molecular structure and functional groups and to define and apply criteria by which results of toxicity tests are considered positive, negative, or questionable.

Several of the priority-setting schemes fail to specify the tests that were actually used for assigning scores. Instead, they merely categorize tests as short-term or chronic. That acute toxic responses may mask chronic effects at high doses is seldom discussed with the criteria for interpretation of oncogenicity studies, although this can be important in distinguishing between close members of a chemical class and can affect the degree of concern given to common features of chemical structure.

None of the schemes reviewed incorporates factors that permit distinctions concerning the role of a chemical in carcinogenicity (e.g., whether initiator or promoter), although this may influence the degree of concern attached to activity of particular structural types. Furthermore, most schemes do not use data on genotoxicity as an aid in making such interpretations.

QUANTIFICATION OF POTENTIAL HARM

The assessment of potential harm is confusing in some of the schemes, where point estimates of toxicity are interchanged with estimates of their uncertainty. In one case, the problem arises where default values for missing data are combined with estimates, without attention to the differing degrees of uncertainty about each. In another case, "strong" evidence is scored with positive numbers and "weak" evidence with negative numbers, without explaining how the two types of information should be aggregated in the priority-setting process. Information on arithmetic "means" is combined with information on "variances," without sufficient attention to how each contributes to the value of information and to the indicator of potential harm. Several of the schemes avoid the confusion by taking into account the degree of uncertainty attached to various point estimates. About half the schemes have essentially no consideration of reliability or uncertainty of information, other than assertions that the input data are of poor quality.

OUTPUT OF THE PRIORITY-SETTING PROCESS

Some of the schemes produce only one list, in order of "priority." Others produce several lists; the chemicals in these lists are sometimes ranked in order of importance, sometimes not. In at least one scheme, the output is in the form of lists of unranked chemicals, which are to be processed further by "expert committees." However, guidelines and criteria for such expert committees are generally lacking.

Seven of the schemes are designed specifically to produce testing recommendations (Astill et al., 1981; Cramer et al., 1978; Dehn and Helmes, 1974; Food Chemical News, 1980; Gori, 1977; Nisbet, 1979; Ross and Lu, 1980). The other three either include testing as one possible decision or provide information that could be used for a testing decision (Brown et al., 1980; Kornreich et al., 1979; Wilhelm, 1981).

SCIENTIFIC SOUNDNESS

The schemes all demonstrate, to one degree or another, the difficulty of maintaining a scientifically defensible procedure in the face of severely deficient data and severe resource constraints.

In application, some schemes appear rigid and mechanical, some highly judgmental and discretionary. All are highly judgmental in construction. As a general pattern, schemes that start with long lists tend to be mechanical, at least in the first sortings. They tend to become more judgmental as the lists become shorter.

It appears to be a general pattern to make deletions from the list of suspect chemicals first on the basis of exposure and later on the basis of suspected nontoxicity. There is no explanation for this sequence, but it may be based on cost considerations. It seems to be presumed that the gathering of exposure data (or the surrogate, production-volume data) is less expensive than the gathering, or generation, of toxicity data and that the inexpensive exposure data are more reliable, more valuable, or more rapidly obtained than toxicity data of the same cost.

Some of the priority-setting processes are more flexible than others. One, for example, is based on a fairly rigid lexicographic ordering principle. To compensate for this rigidity, there are routes for re-entering deleted chemicals in the list for further processing. Thus, it is possible to characterize schemes according to how many options they provide in setting priorities.

There is little explanation of the grounds for designing the structure of any of the schemes. In general, however, there is some discussion of principles at the beginning of the description of each scheme. The scheme is then presented with only minimal explanation of how the principles led to the particular decisions embodied in the scheme. In some schemes, applications appear to be derived from principles; in others, the reverse process seems to have occurred.

PERFORMANCE EVALUATION AND VERIFICATION

There appears to be no provision for performance evaluation in any of the schemes. This is in contrast with procedures in the private sector for setting priorities for research and development projects, which generally include at least informal checks of performance and concern for improvement over time. Some of the schemes are designed as though they were to be applied only once, with no chance for improvement. Others discuss ways in which they might be improved through experience. But none sets up ways in which performance can be verified--an important condition for improving a process through experience. At least one scheme discusses the need to develop better predictions based on structure-activity relationships, but it does not discuss how to do it. Several of the schemes make point estimates of potential toxicity, and some make probabilistic predictions of toxicity; the latter could be checked for performance. Others, with a mixed notion of "concern," are probably impossible to check for performance.

RESOURCE REQUIREMENTS

There is considerable attention in all the schemes to the cost of obtaining and processing information. If a scheme is to be applied to a large number of chemicals, only a small investment of resources can be devoted to each one. If a scheme is to be applied to a small number of chemicals, it can afford to commit more per chemical. Thus, some schemes are designed to work on large volumes (20,000-70,000 chemicals) and emphasize computer processing of machine-readable data to reduce very large lists to much smaller lists; and some schemes are designed for small groups (50-400 chemicals) and require extensive reading and evaluation of literature on toxicity and exposure for each chemical.

None of the descriptions included the cost of developing or operating a scheme on a per-chemical basis. On the basis of limited consulting with the developers and our judgment as to the difficulty of implementing the schemes, we estimate that they require an average of several minutes to several days of professional effort per chemical. Because all are designed to operate on a volume of at least hundreds (and probably thousands) of substances, higher costs may not be justifiable when available funding is considered.

Costs, in general, seem to be appropriate to the job to be done, in that coarse screening of long lists of substances usually entails smaller per-chemical resources. However, some systems seem to include a reduction in scientific credibility without compensatory cost savings.

A priority question that does not appear to be addressed by any of the schemes is the allocation of resources between priority-setting and testing. None of the schemes addresses this question explicitly, but there seems to be a rule of thumb: the designers of the schemes generally attempt to hold the total cost of the priority-setting process to a very small percentage of the budget for testing. This rule of thumb, not included in any of the schemes, was stated by some of the designers. Presumably, the implicit budget ceiling for priority-setting processes leads to this pattern.

Other cost questions receive little, if any, attention. For example, how much time, effort, and money should be spent on toxicity data, relative to those spent on exposure data? Some schemes spend about 80% of their resources on exposure data; others spend most of their resources on toxicity data. None of the schemes attempts to explain the allocation of resources.

As to the costs of some tests of selected chemicals, relative to the value of the test results, how fast should each priority list be exhausted? A list can be covered more quickly if short-term, inexpensive tests are prescribed than if long-term, expensive tests are prescribed. The matching of tests and lists is an indication of how many chemicals can be put on each priority list. Thus, this matching is part of the priority-setting problem. However, none of the schemes addresses it.

SUMMARY AND CONCLUSIONS

Systems for categorizing substances in terms of relative toxicity or potential public-health impact have been reviewed, with particular reference to the priority-setting needs of the NTP in ranking chemicals for toxicity testing. Although few such systems have been reported in the open literature, a growing number are in use or under development in government agencies and private organizations.

All the systems succeed to some degree in categorizing chemicals of different types in terms of relative toxicity, potential for human exposure, or both, but they have been designed for relatively limited purposes in comparison with the broad mission of the NTP. To cope with the vast number and types of chemicals and toxic effects that must be addressed by the NTP, a more comprehensive and elaborate system, or hierarchy of systems, is called for. Study of the available schemes has helped to identify issues and problems that must be addressed and resolved in the process of designing a maximally effective system for use by the NTP. In designing a priority-setting system for the NTP, the Committee will be guided by the following recommendations:

- The testing strategy should permit gathering of the necessary information in a cost-effective manner, with decisions on the collection of information at each stage in the process based on the value of information.
- A cost-effective balance should be achieved between the resources devoted to the priority-setting process and the testing itself.
- The extent to which lack of information on chemicals is a constraint on their selection and ranking for testing should be recognized.
- The system should contain mechanisms for self-evaluation and for modification to improve performance.
- The role of expert judgment should be clearly described.
- Attention should be given to the advantages of a multistage strategy that might include both screening and sorting in the selection and ranking of substances for testing.
- The system should recognize and take into account the characteristics of toxicity tests, such as rates of false-negative and false-positive test results.
- The system should strive for a proper balance of resources devoted to developing and interpreting exposure information and toxicity information and the sequence in which these are most effectively acquired and used.
- Without being excessive in resource use, exposure assessment should reflect the complexity of real-life exposure situations.
- The system should ensure cost-effective and scientifically sound treatment of the uncertainties in exposure estimates and toxicity estimates.
- The toxicity evaluation process should give adequate consideration to the various types of health effects that different substances might be expected to elicit.

- The system should strive to achieve an effective balance in its use of various sources of toxicity information, such as structure-activity relationships, short-term tests, and literature review; and it should include a mechanism to verify conclusions based on predictive data.
- The system should include strategies for dealing with additive, synergistic, or antagonistic toxicologic interactions that may result from exposures to combinations of substances.

A system of priority-setting for testing ideally should possess the ability to characterize for each chemical in question the available information on toxicity and on relevant exposure of the human population. This information should be reasonably quantified and convincingly qualified. The system should be applicable to the universe of chemicals, the toxic effects, and the testing procedures of concern to the NTP and affiliated organizations. It should be scientifically sound, workable, cost-effective in resource use, and designed to provide for improvement in its capabilities through systematic verification and performance evaluation. Because of the lack of information on most chemicals, constraints on resources, and the need to rely on relatively rigid and mechanical methods for addressing long lists of chemicals, no system can fully meet these objectives. A system for use by the NTP should address these objectives explicitly and meet them to the greatest extent feasible.

In the coming year, the Committee on Priority Mechanisms will seek to develop a priority-setting approach commensurate with these objectives.

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APPENDIX IV-1

Priority-setting procedures reviewed
in detail in this report.

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APPENDIX IV-2

Systems described in detail.

Initial examination of the priority-setting schemes surveyed revealed that the multiplicity of approaches was more apparent than real. The appearance of dissimilarity arises more from differences in emphasis, or scope, than from differences in basic logic or strategy.

Selected for detailed description in this report were schemes that were thought to make important contributions to the developing science or art of priority-setting. The choices in some cases were related to uniqueness in the treatment of exposure, of toxicity, or of the interaction of the two.

The TSCA-ITC scheme (Nisbet, 1979) is of particular interest, because it deals with a large part of the universe with which the NTP is concerned. Equally important, it has had to face the test of continued use over several years, and it has been systematically reviewed (Enviro Control, 1979).

The schemes of Kornreich et al. (1979) and Ross and Lu (1980) are based on a systematic review of a substantial portion of the literature on priority-setting. The FDA scheme (Food Chemical News, 1979, 1980) is limited to one route of exposure, but otherwise is comprehensive in its approach. The scheme of Wilhelm (1981) is in large measure a response to what were perceived as deficiencies in the TSCA-ITC system. That of Astill et al. (1981) is designed to function with a sequential testing and feedback strategy. The ranking algorithm of Brown et al. (1980) is based on a simple mathematical model and is designed for multinational application. The proposed cyclic review procedure for the FDA (1981) uses structure-activity considerations to establish initial "levels of concern," which are also found in the decision-tree approach of Cramer, Ford, and Hall (1978). Gori's scheme (1977) provides a ranking index based on exposure that is complementary to a second scheme that uses structure-activity analysis for assessing possible carcinogenic activity (Dehn and Helmes, 1974).

SEQUENTIAL TESTING FOR CHEMICAL RISK ASSESSMENT (ASTILL ET AL., 1981)

This scoring system was developed by the Eastman Kodak Company to determine the extent of toxicity testing required for production chemicals. Four categories of information are used to derive a total score, on the basis of which one of four testing levels is recommended. Available health and environmental data are compiled and rated independently, composite health-effects scores are computed, and the appropriate tests are selected and performed. Results of these tests are then used to revise the ratings. New scores are obtained and the testing level is revised. This process is repeated until testing information is complete. Thus, the system is dynamic, in that it incorporates a feedback mechanism allowing for continuing review of the testing needs

of a specific chemical. This system thus provides a basis for a multistage screening system.

Four categories of information are used: magnitude of human exposure, magnitude of environmental exposure, effects on human health, and effects on the environment. The two magnitude categories have four components each, and the two effects categories have three components each.

The four components considered in the rating of the magnitude of human exposure are production volume, number of people exposed, hours per year exposed, and number of population types exposed. Scores for the four components are added to yield a value for the magnitude of exposure. The assessment of health effects considers the LD_{50}, acute effects (reversible and irreversible), and chronic effects (reversible and irreversible).

Each of the 14 components for the four categories is scored from 1 to 3, with 3 indicating the most severe or hazardous score. The scores for the two human categories (health effects and magnitude of human exposure) are summed, as are the scores for the two environmental categories. The resulting scores range from 7 to 21 and are associated with specific testing levels, as follows:

Testing Level	Health (or Environmental) Score
I	7-9
II	10-13
III	14-17
IV	18-21

The level of testing becomes increasingly specific and sophisticated with increasing score. Level I testing is based on the use of physicochemical evaluation and health screening, as well as acute-toxicity studies. Although it is not specifically stated, with respect to human data Level I might include surveillance of morbidity, mortality, and fertility patterns of exposed human populations. Level II testing consists of toxicity tests that are intermediate between acute tests and subchronic-feeding studies, whereas Level III testing includes subacute-exposure studies. Long-term (or chronic) health effects are evaluated through Level IV testing.

The health-effects criteria are not very specific, but readily quantified in an objective and replicable manner. The health-effects criteria and ratings are as follows:

		Rating
LD_{50}, mg/kg	> 500	1
	50-500	2
	< 50	3

Immediate effects	None	1
	Reversible	2
	Irreversible	3
Prolonged effects	None	1
	Reversible	2
	Irreversible	3

This system appears to be efficient, in that it uses a minimum of subjective input (expert opinion or judgment), although such judgment may be used in the review and rating of health effects.

This system appears to be practical, in that it facilitates decision-making in an efficient and objective manner. Any compound can be evaluated; in the absence of available data, baseline information is compiled before any testing is done. The baseline information compiled consists of:

- Quantities manufactured and disposed of.
- Exposure estimates.
- Product function and application.
- Structure-activity correlation.
- Literature search.
- Cancer hazard evaluation.

Such baseline information may be sufficiently complete for hazard assessment, particularly if previously published toxicity studies are available.

This scheme has been evaluated by the authors with a wide range of industrial chemicals, although the specifics of evaluation are not provided.

A RANKING ALGORITHM FOR EEC WATER POLLUTANTS (BROWN ET AL., 1980)

The purpose of this scheme is to rank, for possible regulatory action, water pollutants as potential hazards to humans and to aquatic organisms. The scheme considers about 1,500 compounds used in countries of the European Economic Community and suspected of entering rivers.

The algorithm is based on a simplified mathematical model relating production and use of a chemical to occurrence in drinking water and in food of fresh-water origin. Standard assumptions are made as to intake of fish and water; daily maximal and annual average intakes through ingestion are calculated.

The amount of a chemical estimated to reach the water is calculated by multiplying production by the fraction that reaches the water; the fraction is estimated on the basis of manufacturing practices and the chemical's use. A typical dilution volume of the chemical is estimated from its half-life in water and from river-flow data. Estimated concentrations are used to calculate human exposure from consuming

drinking water and fresh-water fish. A concentration factor is used to calculate ingestion from consumption of fish, assuming typical diets.

The list of 1,500 chemicals was reduced to about 1,400 when mercury and cadmium compounds were eliminated because they were already controlled by the EEC. Also eliminated were persistent synthetic substances (mainly plastic materials) that are objectionable in water, but not toxic.

For the remaining 1,400 compounds, production and consumption data are obtained and all those estimated to be produced at under 100 metric tons per year are eliminated. The remaining 426 compounds are then processed through a screening algorithm based on production, environmental half-life, and acute-toxicity factors.

Some elements of toxicity testing for human health are applied in this scheme. The acute-mammalian-effect dose is represented by the lowest reported lethal oral dose for humans. If this information is not available, the lowest oral LD_{50} value for other mammalian species is used. If no oral LD_{50} value is available, the lowest LD_{50} value for the dermal or inhalation route is applied. If no LD_{50} values have been reported at all, the lowest lethal dose for the oral, dermal, or inhalation route is used. If no acute-lethality data are available, an estimate is devised on the basis of comparison with other compounds in the same chemical class. If a reasonable estimate cannot be made this way, the default entry "unknown" is used in the program.

Chronic mammalian effects are also used when available. If the data file indicates that carcinogenicity, mutagenicity, or teratogenicity information is available, it is factored into the algorithm. If a compound exhibits all three effects, only one is entered, preferably carcinogenicity. The chronic-mammalian-effect dose is the lowest dose that caused the reported effect.

ESTIMATION OF TOXIC HAZARD--A DECISION TREE APPROACH (CRAMER ET AL., 1978)

This scheme ranks food chemicals in three classes of concern for toxicity testing based on chemical structure and oral-toxicity data. It is applied to structurally defined organic and organometallic compounds. Polymers and inorganic compounds are excluded.

By answering a series of questions about chemical structure, the operator of the system follows a decision tree until the chemical considered falls into Class I (low concern), Class II (moderate concern), or Class III (serious concern). Within each class, chemicals are ranked by comparison with no-observed-effect doses. The data on no-effect doses were derived from literature values based on short-term or chronic studies.

Class I substances are those whose structures and toxicity data, when combined with low human exposure, suggest low priority for investigation. Class III substances are those whose structure and toxicity data would not permit presumptions of safety and which thus require the highest priority for investigation. Class II substances are

intermediate between Classes I and III. High exposures to substances in any class would increase the priority for investigation or testing. The number of chemicals found to be in Class II is not large.

In tabulating compounds within classes, with the exception of compounds with no-effect exposures above 500 mg/kg of body weight per day, the tabulation is restricted to toxicity tests in which the next higher feeding exposure above the no-effect exposure is no more than 5 times the no-effect exposure. It was the general intent of the authors that the most toxic substances in Class I (low concern) should have a no-effect exposure in animal tests at or above 50 mg/kg of body weight per day. This exposure, subjected to a safety factor of 100, corresponds to human exposure at approximately 25 mg/day.

Use of this procedure requires knowledge of chemical structure and reasonably accurate estimates of human intake. The authors made it clear that chemical structure is to be used only as a guideline for testing decisions and that such use of structure-activity analysis is intended as a guide to the acquisition of data, not as a substitute for data.

AN AUTOMATIC PROCEDURE FOR ASSESSING POSSIBLE CARCINOGENIC ACTIVITY OF CHEMICALS PRIOR TO TESTING (DEHN AND HELMES, 1974)

This scheme uses structure-activity relationships to predict carcinogenesis. There is no exposure element. The corresponding exposure element has been described by Gori (1977).

The procedure incorporates the collective knowledge of a panel of experts and attempts to automate the key features of that knowledge to select candidate compounds for carcinogenicity testing. The basis of the procedure is an activity tree constructed so that more specific details of chemical structure (as related to carcinogenicity) are applied at each decision point in the tree. This subdivision of structures continues until an end group (called a node) containing compounds of closely related chemical structure is identified. An estimate is then made of the probability that the chemicals in a node are carcinogenic and of the relative potency of each. Reflecting the expertise of the panel, construction of the tree concentrates on the following groups of chemicals: naturally occurring substances; nitroso, hydrazino, and azo compounds; polycyclic aromatic hydrocarbons; aromatic amines; and inorganic compounds.

Although structure-activity relationships can be useful in setting priorities for carcinogenicity testing, the accuracy of analysis of such relationships in predicting carcinogenicity has not been verified. If the decision tree could be compared with test data generated since the scheme was completed, its utility could be better assessed. Exceptions within a given node (i.e., negative compounds within a carcinogenic chemical class) are extremely instructive and should serve as a cautionary guide when one attempts to apply analysis of structure-activity relationships in too broad a manner.

CYCLIC REVIEW OF DIRECT FOOD ADDITIVES
(Attributed to Food and Drug Administration
by Food Chemical News, 1979, 1980)

This scheme is being developed to establish priorities (and extent) for toxicity testing of direct food additives.

Chemicals are divided into three categories of suspicion based on structure-activity considerations, by following a short decision tree. The suspicion category is combined with exposure information to define a level of concern (I, II, or III). Once the level of concern is determined, tests may be required. The existing studies are placed in three categories (well done; not well enough done, but usable to some degree as a "core" test; and unusable). On the basis of this further information, additional testing may be required.

Toxicity is not estimated quantitatively, so there is no quantitative assessment of uncertainty for it. There is judgmental consideration of uncertainty (specification error) in the evaluation of toxicity tests in the literature.

There is a discussion of tests for each level of concern and for various combinations of concern and test information.

RANKING OF ENVIRONMENTAL CONTAMINANTS FOR BIOASSAY PRIORITY
(GORI, 1977)

The purpose of this scheme is to establish a priority ranking for chemicals to be tested in a carcinogenicity bioassay, based on exposure. All chemicals in commerce are considered by the scheme. Total intake of a chemical by a given route is estimated for all members of a population group with similar exposures; intake is then summed over population groups and sources of exposure. Intake by route is then combined with probability of carcinogenicity and expected potency to produce a ranking index that, in theory, reflects the expected annual number of cancer cases.

The scheme depends on the quantitative prediction of carcinogenic activity from structure-activity comparisons (see Dehn and Helmes, 1974). This requires the identification of substructures, derived from known carcinogens, to which activity indexes can be attached--a process that requires expert opinion. A chemical of unknown carcinogenic potential is then inspected for such substructures, and an activity value is ascertained on the basis of their presence.

Exposure assessment takes account of chemical production and use, but not disposal or discharges explicitly.

Although it may not be clear from the text, the scheme estimates an uncertainty factor or confidence range for every variable. One notes and keeps track of the route of exposure and maintains an "audit trail" to the information in the data base.

Deriving an exposure estimate for a chemical might require up to a person-day of effort, on the average. Considerable subjective input is required.

PRIORITY SETTING OF TOXIC SUBSTANCES FOR GUIDING MONITORING PROGRAMS (KORNREICH ET AL., 1979)

This system, prepared for the Office of Technology Assessment by Clement Associates, is designed to compile a priority list for selecting potentially toxic chemicals for monitoring in food.

The criteria used in developing 32 existing priority lists of toxic chemicals are examined, and criteria developed by which chemicals are ranked on the basis of their likelihood of endangering human health through contamination of the food supply. Three preliminary lists of possible food contaminants (organic substances, inorganic substances, and radionuclides) are compiled. Data are assembled on each chemical on these lists and used to assign scores to each chemical for various factors. Scores for the factors are combined, and the combined scores are used for ranking the chemicals on the three lists.

Selection criteria include both exposure and toxicity factors. Weights are assigned to reflect the relative importance of each criterion and to allow the total score to be a measure of the overall propensity of a chemical to contaminate foods. The individual score for each factor is multiplied by the assigned weight, and the weighted scores are added. The total exposure score and the total biologic score are each adjusted to a maximal score of 50 points and summed to allow for a possible total of 100 points.

This system is designed to use quantitative information, with considerable reliance on expert opinion for the assigning of scores. For toxicity factors, a score of 0 is assigned for negative results and for absence of data.

No cost estimates are given for this system, which was intended for one-time, rather than repeated, use.

RANKING CHEMICALS FOR TESTING: A PRIORITY-SETTING EXERCISE UNDER THE TOXIC SUBSTANCES CONTROL ACT (NISBET, 1979)

This scoring system was developed to set priorities for testing chemicals under the authority of the Toxic Substances Control Act (TSCA). The scheme is intended for application to chemicals in commerce that are not covered by other statutes. Drugs, cosmetics, food additives, and pesticides are excluded, unless they also have other uses. Also excluded are chemicals with an annual production volume of 1,000 lb or less. The system is intended for chemicals already in commerce at the time of compilation of the TSCA Inventory, which now defines "old" chemicals for the purposes of the statute. Because the inventory did not exist when the first testing recommendations were required by the statute, the system was originally applied to a list of chemicals derived from existing lists of chemicals of high production volume or previously reported toxicity. Thus, the initial "universe" of chemicals was limited to chemicals already identified as of potential concern or nominated for inclusion by ITC members or other experts.

Of 24 priority lists reviewed, 19 were used as a basis for the initial compilation of compounds. Noncommercial chemicals were then eliminated. Chemicals that were not on the U.S. International Trade Commission list were designated to be eliminated from the list, but were screened initially and were included if nominated by the expert panel. Later screening evaluated use and eliminated substances already regulated under some statute other than the TSCA.

These initial screening steps resulted in a list of approximately 900 chemicals for scoring. The ITC divided the scoring process into two discrete phases--potential exposure and biologic effects. Screening and scoring of biologic effects were postponed until potential exposure was evaluated. The following factors were used in the first stage of exposure scoring:

- General population exposure--number of people exposed, frequency of exposure, exposure intensity, and penetrability.
- Quantity released into environment--quantity released and persistence.
- Production volume.
- Occupational exposure.

Some 330 chemicals were then selected from the list for biologic scoring. The TSCA requires that the ITC give priority to compounds that are known or suspected to cause or contribute to cancer, gene mutations, or birth defects. Seven factors were selected for scoring on biologic activity:

- Carcinogenicity.
- Mutagenicity.
- Teratogenicity.
- Acute toxicity.
- Other toxic effects.
- Ecologic effects.*
- Bioaccumulation.

Because the ITC seeks to identify chemicals that require testing, rather than simply scoring compounds for known biologic activity, it was decided that the biologic scoring system should have two independent components--a measure of known biologic activity and a measure of the need for further testing. These components provided the basis for the biologic scoring system, as follows:

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*Note that this scheme and its variants (Enviro Control, 1979; Ross and Lu, 1980) are designed to set priorities among chemicals for potential effects on the environment, as well as on human health.

Positive numerical score 1 to 3:

- Substance does not need further testing.
- The higher the number, the more positive the results.

Zero score:

- Negative test results.
- Biologically inactive compound.
- Low index of suspicion.

Negative numerical score -1 to -3:

- Lack of data--substance should be tested further.
- The more negative the number, the greater the need for testing (as judged by other data on biologic activity or data on structural analogues).

Early in 1979, the ITC sponsored a workshop to review the ITC system and to make recommendations for improvements. The proceedings of the workshop (Enviro Control, 1979) includes a number of papers on priority-setting systems and reports by 11 subgroups that reviewed different elements of the ITC scoring system and recommended changes in scoring methods for individual exposure and toxicity elements. The workshop did not propose a comprehensive alternative scheme and did not produce a synthesis of the recommendations of the subgroups.

CHEMICAL SCORING SYSTEM DEVELOPMENT (ROSS AND LU, 1980)

This draft scheme is designed to screen relatively large numbers of chemicals and to identify those with the greatest need for control or testing. The scheme considers subsets of the TSCA Inventory, including chemicals on which the EPA expects to receive additional production- and exposure-related information under section 8(a) of TSCA.

The scheme consists of several scoring processes grouped into five components: biologic toxicity I, biologic toxicity II, environmental fate, production and release, and human exposure. There are several criteria for each component. Each criterion is assigned a numerical score from 0 or 1 to 9 or 10.

Application of the scoring system to chemicals on the TSCA Inventory is in two phases. The first phase screens chemicals into groups of low, moderate, and high concern on the basis of exposure characteristics (production volume, environmental fate, potential environmental release, and potential human exposure). For chemicals that have similar scores on these major exposure criteria, scores on a group of modifier criteria can be applied to determine which compounds have the greater exposure potential. These modifier criteria can receive a maximal score of 9 and

are to be used only in case of ties in the scores on the primary exposure criteria.

The second phase separates chemicals into groups of low, moderate, or high concern on the basis of potential toxic effects. Chemicals that are identified as being of "high concern" in the first phase are to be considered first in the second phase.

The biologic-effects criteria are divided into two categories: biologic toxicity I includes carcinogenicity, mutagenicity, embryotoxicity and fetotoxicity, and reproductive effects; biologic toxicity II includes all other criteria for biologic effects and contains effects on plants, bacteria, fungi, and aquatic organisms. The authors stated:

> Biological toxicity is divided into 2 components because the areas of health effects in the biological toxicity I component are of particular societal and regulatory agency interest and therefore warrant consideration separate from other aspects of toxicity. Another difference between the biological toxicity I and biological toxicity II components is that the scoring systems in the biological toxicity I component are not dose dependence [sic] but are based on expressions of confidence, whereas the scoring systems in the biological II component are either dose or concentration dependent.

In the carcinogenicity scoring process, a precursor is defined as "a chemical which in itself is not carcinogenic but which is responsible for the formation of a chemical which is carcinogenic, e.g., a metabolite." However, the precursor is assigned a score of 4, rather than a potentially higher one.

This scoring process is strictly qualitative and does not deal with the potency of a carcinogen. It appears that absence of data is considered to imply low priority; "no data but suspect" is given a score of 3; "no data but not considered suspect" is given a score equal to that for "no data available, no estimate made."

The mutagenicity scoring procedure considers the potential for genetic impairment at both the somatic cell and germinal cell levels. Like the carcinogenicity scoring procedure, it is strictly qualitative, and a suspect chemical on which no data are available will score low (2 or 3).

Several types of prenatal effects are combined under the broad terms of "embryotoxicity" and "fetotoxicity." Whether other reproductive effects are distinguished from true teratogenic action is unclear.

The chronic-toxicity scoring procedure has two notable components: first, it scores on the basis of quantitative dosage criteria; second, it scores on the basis of the severity of an effect. No guidelines are given to indicate what specific effects would be examined or called for. Again, suspect chemicals with no data get low scores.

The acute-toxicity scoring system considers lethal end points, but not functional impairment. Several opportunities for scoring are possible, because data from any route are considered. When several routes have been studied, the data that provided the highest score are used in the final priority-setting. Chemicals "suspected to have a score of 8 to 10" are assigned a score of 3 when there are no data to confirm the suspicion. Again, suspect chemicals with no data get low scores.

The first phase of the screening program uses the "exposure" component and subcomponent scores to screen and set testing priorities for chemicals on which additional biologic-effects data are needed. The actual priority-setting treats the data as a set of component scores (for either exposure or biologic effects) that are made up of combinations of subcomponents. Each component has a maximal score of 10. The ratio of the assigned score to the maximal score is displayed. If any subcomponent receives a score of 10, it is automatically placed in a rank of high concern. Otherwise, the accumulated subcomponent ratios within a component are assigned scores and a hazard index is calculated.

Subcomponent scores are added and form the numerator of a fraction whose denominator is the sum of possible scores for each of the subcomponents within the component. A hazard index is the expression of the ratios as a percentage. With the exception that a score of 10 in any subcomponent automatically places that chemical in a category of high concern, the hazard indexes for each component are to be used to place the chemicals in categories of high, moderate, or low concern.

SELECTING PRIORITIES FROM LARGE SETS OF ALTERNATIVES: THE CASE OF TOXIC SUBSTANCES REGULATION (WILHELM, 1981)

Although it is not explicitly stated, this scheme seems designed to rank the TSCA Inventory list of chemicals for further toxicity testing.

Seventeen scores are developed per chemical. The author argued against using any single aggregation function for these scores. Instead, he suggested nine aggregation functions, each designed for a special purpose (picking out regulatory targets, establishing testing priorities by ranking chemicals on the basis of volume and suspicion of toxicity, possible environmental problems, possible occupational problems, and suspicion of toxicity based on chemical structure). These aggregation functions are defined in terms of inequality constraints on the summary scores.

A score for exposure potential is derived from a simply calculated function of production volume. Factors for exposure potential are production volume, number of chemical-plant sites, and estimated number of workers exposed. The data are to be read, and processing performed, by computer.

Indicators of suspicion are expressed as a series of 10 scores that are reduced to three summary scores. Each score refers to the number of lines in the RTECS file on an item of interest--total number of

toxic-dose lines, number of reviews (one each line), number of toxic-dose lines that deal with teratogenic, carcinogenic, and mutagenic studies, etc.

Further indicators are developed for closely related chemicals, and searches are made for toxic-element components for the chemical in question.

The summary scores appear to depend heavily on quantity of information, as contrasted with quality of information. For example, the human-toxicity score is 1 if there is one line in RTECS on human toxicity and 5 if there are five lines. Scoring by the number of lines in RTECS ignores both the nature and the quality of the published data.

In defense of this approach, it is hard to imagine schemes capable of processing the 55,000 TSCA Inventory chemicals without severe simplifications. Examining the whole list of chemicals requires the use of simple indicators that almost inevitably treat some unequal things as equal.

Because of the simple and mechanical nature of the scheme, it might be most useful as one part of a larger scheme. Its role would be to scan the entire universe of chemicals and to put those most in need of testing on a series of (relatively) short lists. Each list could be augmented or reduced by other methods.

The author believed expert judgment to be essential. The experts are to make decisions from the shorter lists generated by the aggregation functions working on the summary of scores from the entire universe of chemicals. The scheme does not describe how the experts are to perform this role.

The scheme is designed to use quantitative information. Qualifications come at the level of expert judgment, once the lists are obtained, and at the level of discussion that motivates the particular scores and summaries. These qualifications would be more convincing if the scheme were placed in the context of a larger scheme of priority-setting that explained how expert judgments were to be used and how the short lists could be augmented by other means that might compensate for possible weaknesses due to the simplifications inherent in this scheme.

The principal virtue of this scheme is its moderate use of resources. It would be useful to have some estimates of what it would cost in time, money, and personnel to implement the scheme for the full 55,000 chemicals.

The scheme appears to be well designed for a narrow, but highly important, role in a larger priority-setting scheme.