# Priority Setting of Toxic Substances for Guiding Monitoring Programs *

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## INTRODUCTORY REMARKS ON THE ESTABLISHMENT OF PRIORITIES

There are many purposes for which the Federal Government must set priorities among toxic chemicals in the environment. The universe of environmental contaminants is very large, and resources for research, testing, monitoring, and regulation are limited. Some statutes explicitly require Government agencies to set priorities for testing or regulation, and in many other cases agencies may be called on to explain their decisions to tackle some problems before others. Accordingly it is very desirable to develop rational systems for setting priorities.

Establishment of priorities involves preparing a list of problems, ordered according to their perceived *'importance" or urgency, before attempting to solve them. It is by definition a preliminary step and should be designed to maximize the efficiency of the problem-solving process, Although it is desirable to use as much relevant information as possible in setting priorities, it is also possible to use too much information. If too much time is spent in overelaborate priority-setting exercises the gain in efficiency achieved by tackling the most urgent problems first is offset by a delay in taking any action at all. The first task in designing an efficient priority-setting system is thus to make a reasonable compromise between the effort expended on this preliminary step and the gain in efficiency achieved by doing it well.

Priority-setting exercises are usually limited primarily by the unavailability of data. (If extensive data are available, then it is usually obvious which problems should be tackled first. ) For this reason there is usually little to be gained by developing elaborate multifactorial schemes to rank problems in numerical order. Good systems for establishing priorities will inevitably involve a substantial element of sound scientific judgment in weighing and interpreting incomplete and unsystematic data. The second task in designing an efficient priority-setting system is thus to make a reasonable compromise between the use of objective criteria and scientific judgment.

This report is concerned specifically with the establishment of priorities for monitoring toxic chemicals in food. There are two general methods by which this might be done: 1) directly, by sampling the food supply for chemical contaminants and ranking them according to potential hazard; and 2) indirectly, by surveying the universe of industrial chemicals and ranking them according to their potential for entering the food supply in toxic amounts. The first method has obvious advantages and in fact has been pursued by FDA. The method is, however, limited by the available analytical methodology: specifically, most of the chemicals recognized to date as food contaminants are those relatively easily detected by gas chromatography or atomic absorption spectrometry. The principal question addressed in this report, therefore, is whether the second method can complement the first by identifying potentially significant contaminants that have not yet been detected in foods. Although this report indicates that it can do so, it should be recognized that the second method also is limited to some extent by available analytical methodology. The factors we can use to identify the potential of a chemical for entering the food supply are selected on the basis of a knowledge of the properties and environmental behavior of other chemicals already known to do so. This in turn is based on our knowledge of the extent of contamination and hence on our analytical capabilities. Thus, there is an inherent bias towards identifying as potential food con-

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taminants those chemicals that are similar to chemicals already identified in food. This bias can only be offset by the use of good scientific judgment. This point illustrates a general problem in all systems for setting priorities: chemicals on which there is no information at all will automatically be given low priority, unless some room is left for largely intuitive judgments,

# CRITERIA AND METHODS USED IN PREVIOUS EFFORTS TO ESTABLISH PRIORITIES AMONG TOXIC CHEMICALS IN THE ENVIRONMENT

## Survey of Toxic Chemical Priority Lists

Thirty-two priority lists of toxic chemicals compiled during the last 5 years have been identified. Most of these lists (28 out of 32) were prepared for the Federal Government. For each list, a description sheet indicating the purpose of the list and the criteria used in selecting chemicals was prepared. In addition, the name of the list, the Federal agency or other institution for which the list was compiled, the date of completion, the contract or document number, type of substances, the number of chemical substances, the means by which the chemical was identified (for example, CAS number or chemical name), whether the list is machine readable, and relevant comments were included.

## Methods

### Chemical Selection

Compiling a comprehensive list. The first step in priority-setting efforts is usually compilation of a comprehensive list defining the universe of chemicals under consideration. Since chemical compounds and mixtures are often referred to by several different names, each chemical compound on the comprehensive list should be uniquely identified. This can be done by specifying for each chemical on the list the IUPAC chemical name, synonyms, molecular structure, and/or the Chemical Abstracts Service (CAS) registry number. The use of CAS numbers facilitates computerization.

Most often, the source of chemicals for this comprehensive list is previously existing lists. Errors of omission are likely with this method. A chemical not considered previously will not be considered by someone using existing lists as a source, The more comprehensive the source lists, the less likely chemicals are to be omitted from consideration. An alternative method for selecting chemicals for consideration is reliance on recommendations of experts. The likelihood of errors of omission when this method is used will depend on the extent of knowledge and experience of the experts. These methods can be combined by supplementing source lists with chemicals of concern to experts.

Reducing the size of the comprehensive list. It is almost always necessary to reduce the size of the comprehensive list before ranking. Since the resources needed for compiling and evaluating the necessary data for setting priorities are usually limited, a “narrowing” or “truncating” step is performed. Errors are very likely to occur at this step because, for practical reasons, decisions at this stage are usually based on incomplete information, In a multistage priority selection scheme, such as the one by which the TSCA Interagency Testing Committee selected chemicals to recommend to the EPA Administrator for testing, additional information is obtained at each stage of reduction. In that effort, an initial listing of 3,650 substances was reduced to a master file of 1,700 substances, then to a preliminary list of 330 substances from which approximately 100 chemicals were selected for dossier preparation. Twenty-one chemicals or groups of chemicals from that list have been designated for recommendation by the committee. In this type of process, the earliest stages may be the most subjective and the most likely to result in errors of omission.

Grouping. Individual chemicals are often combined in groups or classes. This is usually done in an attempt to reduce a list of chemicals to a more manageable set, There are, however, other reasons for grouping. Some monitoring or analytical techniques do not distinguish between closely related chemicals. Some classes of chemicals, such as fluorocarbons, may be considered as a group for regulatory purposes. Such chemicals as PCBs are not manufactured or used as individual chemical compounds and are, therefore, nearly always considered as a group. Groups can be based on chemical and physical properties, on chemical

structure, on uses (e.g., flame retardants, fluorescent brighteners), or on some combination of these factors. Sometimes a single compound or several compounds are selected as representative of the group.

An advantage of grouping chemicals with similar structure or functional groups is that it sometimes allows chemical, physical, and biological properties of individual compounds to be predicted. Members of a chemical class may behave in a qualitatively similar fashion. In addition, some properties increase or decrease systematically along homologous series. Attempts to derive structure-activity correlations are much more likely to be successful for chemical and physical properties than for biological properties. Because of some unique properties of biological systems, such as enzyme specificity, it is possible for closely related chemical compounds, even such stereoisomers as aldrin, dieldrin, and endrin, to have very different biological properties.

Some weaknesses associated with grouping are:

- Members of the group may vary widely with respect to the factor being scored, making it difficult or meaningless to assign a single score to the group.
- No single compound can truly represent an entire class.
- It is often difficult to assign compounds with several different functional groups to a single chemical class. This difficulty can sometimes be overcome by computerized substructure search systems that allow all chemical compounds with a specific functional group to be retrieved regardless of the presence or absence of other functional groups.

At one stage of the National Science Foundation (NSF) Workshop Panel, multistage effort grouping was done in an attempt to reduce the list of chemicals to a more manageable set. Fourteen chemical classes were defined, and a representative chemical was identified for each. Weaknesses the panel found to be associated with this procedure included:

- The classes were not completely valid either chemically or functionally.
- The physical and biological properties of compounds in a given class varied widely.
- No single compound was truly representative of a class.

The class concept was abandoned in the next stage of the effort and selected members were considered as individual chemicals.

## Determining Factors To Be Considered in Setting Priorities

The purpose for which the list is to be used must be clarified. Once the problem the priority list is intended to solve is understood, factors relevant to that problem can be determined. Criteria based on those factors can then be formulated for assigning chemicals a place on the list. General criteria must often be defined in terms of specific parameters for which information is available. Those parameters for which quantitative data are readily available are the easiest to use for scoring and ranking. On the other hand, data are frequently lacking on the factors of greatest relevance to the specific problem. In such cases factors of less relevance may have to be selected. The choice of factors to be used in setting priorities often involves a compromise between the factors that are most relevant and the factors on which sufficient information is available.

## Assembling Data on Each Chemical

Sound decisions on assignment of priorities require reliable data on each chemical to be ranked. The available information may, however, be massive, contradictory, unverifiable, scanty, or absent. It is usually difficult or impossible to obtain existing information that has been classified as proprietary or confidential.

When information is needed on a large number of chemicals and only a limited amount of time or money is available for assembling data, secondary sources are usually relied on. Certain types of information (e. g., annual production volume, $LD_{50}$, octanol-water partition coefficients) are often tabulated in secondary sources. Other types of information (e.g., fate and transport in the environment, metabolic pathways) may be obtainable only from primary reports of research studies. These individual studies require considerable time and effort to locate, obtain, and review. In a multistage screening process, primary sources may be used only in the last stage, when the number of chemicals has been reduced to a small portion of the comprehensive initial list. In a very limited effort, primary sources may not be used at all.

## Assigning Priorities

Two general methods used for assigning priorities to toxic chemicals are the ranking of individual chemicals [or classes) and the assigning of individual chemicals (or classes) to priority categories. Only 6 of the 32 lists surveyed are actually ranked. In most of the other lists, chemicals were

either assigned to a single "high priority" category or distributed among several priority level categories.

Some numerical index or score is nearly always used for ranking and often used for assigning chemicals to priority level categories. When chemicals are to be ranked solely by parameters for which comparable quantitative information is available (e.g., oral $LD_{50}$ in the rat or annual production volume) these data can be used directly. When the criteria for ranking cannot be defined in terms of parameters for which comparable quantitative information is available for all chemicals under consideration, chemicals are usually assigned scores. Scoring is also usually used when quantitative and nonquantitative factors are jointly considered for ranking.

The scoring process involves assigning numerical values to one or more parameters to produce an index or series of indices for each chemical. Indices can then be weighted and combined to produce a single score for each chemical,

Scoring can be totally subjective, totally objective, or somewhere in between, Subjective scoring involves the use of experts to assign priorities. The experts may be provided with information on each chemical or may simply be asked for their opinion. The credibility of subjective scoring will depend on the perceived expertness of panel members. Delphi techniques can be used to improve the validity or rankings, Scoring systems based on the Delphi method rely on the development of consensus among experts acting independently or as part of a panel. In the NSF Workshop Panel effort to select organic compounds hazardous to the environment, panel members identified chemicals of concern on the basis of their own experience and refined their judgments by considering available data for production, imports, uses, disposal, and toxicity. Through successive examinations by panel members, individually and together, in progressively greater detail, a priority list was developed. A weakness of such subjective scoring methods is their probable lack of reproducibility, which exists because different experts would be likely to reach different conclusions, (However, we know of no investigation of the reproducibility of such results in which different groups of experts were asked to assign scores to the same chemical s.)

Where scores can be assigned to specific values of parameters for which quantitative information is available, objective scoring may be preferable. Often, however, modifying factors may make the use of some degree of subjective judgment desirable in the assignment of scores even where quantitative information is available. For example, the octanol-water partition coefficient can be used as an index of bioaccumulation, but a more sophisticated scoring system would consider such other factors as chemical reactivity, metabolic fate, and vapor pressure of the compound.

The human health hazard posed by a chemical substance is a function of exposure to the substance and the inherent toxicity of the substance itself. Scores for various exposure and toxicity factors are usually combined for hazard-ranking purposes, No consensus has yet been developed, however, as to the optimum algorithm for hazard ranking in this way.

Linear weighting schemes are efficient and easy to use, and they have produced reasonable results. These schemes rely on the assignment of scores to a number of factors. Weights are assigned to each factor, and the weighted factor scores are summed to produce an overall score for the chemical. The choice of weight is usually a subjective judgment, involving consideration of both the importance of each factor and the reliability of the information used in assigning the score.

Multiplication of individual factor scores provides a wider spread of overall scores, Multiplication is frequently used with actual unscored quantitative data. This is especially likely where some of the data are in the form of fractions. For example, fraction of production lost would be multiplied by total production or fraction of dose absorbed would be multiplied by total administered dose. Multiplication cannot be used unless some correction is applied to allow for data gaps. In the development of one list, an algorithm for toxicity was applied which compensated for types of toxicities for which data were unavailable. The scores actually assigned to a chemical for various categories of toxicity were summed [T(total)]. The maximum toxicity possible for each of these categories for which data were available were also summed [T(possible)]. The ratio of these sums [T(total) ÷ T(possible)] was used as the toxicity factor in the hazard-ranking algorithm. The hazard-ranking algorithm used for ranking manufactured organic air pollutants was:

$$P \times {}^{?}pl \times V \times [T(total) \div T(possible)] = Sf$$

where P = score for annual production
?pl = score for fraction of production lost
V = score for volatility
T(total) = maximum toxicity score possible for those categories of toxicity for which data are available
T(possible) = sum of maximum scores for each of the factors used in compiling T(total)
Sf = final score for hazard ranking

In some cases the scores assigned to certain factors are logarithms of data or are selected subjectively in such a way as to approximate logarithms. In such cases, addition of the scores achieves the same result as multiplication of the actual data. Weighting of the factors before addition then corresponds to changing the base of the logarithm.

## Criteria

The two general criteria used for assessments of health hazard are exposure and toxicity. Previous efforts to set priorities among toxic chemicals in the environment have been reviewed, and specific criteria used to assess the extent of exposure to these chemicals or the toxicity of these chemicals have been considered.

### Exposure

The three aspects of exposure that are of greatest importance in hazard ranking are the number of people exposed, the frequency of exposure, and the quantities of the chemical to which they are exposed. Where direct information is available on these exposure factors, e.g., from monitoring of the ambient environment, of food, or of human tissue, it is obviously desirable to use this information. In most cases, however, we do not have direct information regarding the amount of a chemical to which members of a population are exposed, so that we must rely on indirect information, Several factors have been used, alone or in combination, as surrogates for direct measures of exposure.

Production.—The most commonly used index of exposure is the annual production volume. Since this information is quantitative, it is easy to use for scoring or ranking. In most cases, production volume does provide a rough indication of the amount of a chemical substance potentially available for release into the environment. However, the fraction actually released may vary over several orders of magnitude, from less than 0.001 for well-contained industrial intermediates to 1 for chemicals which are used dispersively.

For organic compounds produced by three or more manufacturers and produced in volumes greater than 5,000 lbs, production information is compiled in the annual reports of the International Trade Commission and is easily available. production information can sometimes also be found in other literature sources or obtained from manufacturers or trade associations, but it is not easy to acquire and will be missing for a large number of chemicals. Production data for chemicals produced by less than three manufacturers are considered proprietary. In the near future, the EPA Toxic Inventory List, being prepared under section 8 of the Toxic Substance Control Act, may be a convenient source of production information, but at this time it is not clear how much of this information will be released to the public.

In addition to annual production volume, data on production capacity, transport volumes, imports, exports, net sales, or levels of consumption may sometimes be available. A major problem with using any of those figures as indices of environmental exposure is that these figures are based on commercial production and sales. The amounts of a chemical used as a captive intermediate are not included although such a chemical may be an occupational health hazard or a neighborhood pollutant in the vicinity of the plant. Very toxic and highly reactive chemicals are often manufactured at the same plant in which they are used. Manufacturing byproducts may never enter commerce but because they are waste products they are very likely to be released to the environment in plant emissions and in effluents. Toxic chemicals formed in the environment (byproducts of microbial degradation or photochemical reaction) also will not be reflected in production figures.

For naturally occurring chemical substances, such as heavy metals, the most relevant parameter is not production, but transfer from one compartment of the environment to another or conversion from one chemical or physical form to another. Such transfers are measures of the increase in the amount of the substance converted into a form in which it is potentially available for human exposure.

Occurrence in the environment. Actual measurements of chemicals occurring in the environment are available for only a small number of substances. Federal agencies tend to monitor on a regular basis only when required to by law. Air pollution measurements are available for carbon monoxide, total hydrocarbons, nitrogen oxides, sulfur oxides, total suspended particulate, and photochemical oxidants. Water pollution monitoring data are available primarily for pesticides, PCBs, and heavy metals. Monitoring information in Government data banks is often not retrievable in readily usable form. There may be a timelag of several years before a Federal agency summarizes, analyzes, and reports monitoring data. For qualitative or quantitative data on occurrence in the environment of chemicals not included in

monitoring programs, it is necessary to search the literature for individual studies. Since these studies will usually report data for a small number of samplings at a limited number of locations (often one), they are difficult to use as a basis for the comparisons needed for ranking chemicals. The number of reported incidents of environmental occurrence will often be a function of interest in the compound rather than of actual frequency of occurrence.

An advantage of using this type of information, when available, is that it provides direct evidence that the chemical is an environmental contaminant.

Use. Patterns of use can be very useful indicators of potential for human exposure. A greater exposure risk is usually associated with dispersive uses than contained uses. Contained uses are those in which the chemical is not systematically released to the environment as a direct result of use (e.g., PCBs in transformers). In dispersive uses, chemicals are released to the environment as a direct consequence of use (e.g., pesticides, aerosols, and volatile solvents). The size of the population at risk is usually greater for consumer uses than for commercial or industrial uses. The class of the use (e. g., food additive, pesticide, or drug) will often determine which Federal agency has regulatory responsibility for a chemical. The use pattern will be a major determinant of the type, frequency, and amount of human contact with a chemical substance.

Unfortunately, accurate, complete, and up-to-date use information is very difficult to acquire. Many industrial uses are considered "proprietary. " Uses can change rapidly so that information compiled in secondary sources is frequently out of date. One problem encountered in using use information is the difficulty of obtaining quantitative data. Since some uses are much more likely to lead to human exposure than others, a quantitative breakdown of uses would be particularly valuable. Even when use data are available, it is important to realize that not all human exposure to chemicals occurs during use. Exposure can also occur during production, formulation, and disposal or after environmental transformation.

Release. The rate at which a chemical substance is released into the environment can be a useful parameter in ranking toxic chemicals. Chemicals that are found in effluents or emissions are most likely to become environmental pollutants. Information on routes of entry of chemicals into the environment can in certain cases be essential to determining population exposure. In 1971 the sole U.S. producer of PCBs voluntarily restricted sales to those for closed-system applications. They assumed that this would minimize risk to human health and the environment. They overlooked the fact that most environmental release of PCBs occurs, not through use, but rather through disposal.

The quantity of a chemical released into the environment is usually unknown so that scores assigned for this factor must be based on estimates. The "release rate" is an interesting index recently developed by the NSF Workshop Panel to Select Organic Compounds Hazardous to the Environment. The release rate (R) was defined as follows:

$$R = (P)L + (P + I)D$$

where P = overall annual U.S. production
I = annual quantity imported
L = fraction of the production lost at plant site during manufacturing, conversion, and formulation
D = fraction of the material which goes to nonintermediate dispersive uses

Estimates of L and D are usually semisubjective, based on knowledge of the manufacturing process and on the likely breakdown of uses.

Environmental transport. A universal or widely dispersed contaminant will usually be given higher priority than a contaminant found only at specific locations or a contaminant whose entry into the environment results from a unique event or sporadic events.

For a persistent chemical, the distinction between a local, widely dispersed, or universal contaminant may be a function of time. Unexpectedly wide transport has been observed in recent years for chemicals such as DDE and PCBs, PBBs entered the environment as a result of a single accidental occurrence and contaminated a small number of Michigan farms. Since these chemicals are persistent and have entered the soil, water, and food supply, they will continue to disperse.

Substances that appear to be relatively innocuous or inert at their point of release may be transported to segments of the environment where they have significant adverse effects. Useful models for the reliable prediction of the movement of chemicals in the environment would be extremely valuable for setting priorities among toxic chemicals for purposes of monitoring, control, or regulation. Such information would also be valuable in determining which segments of the environment should be monitored or controlled. Unfortunately, although models are available for problems such as plume dispersion for stack emissions, there are no generally accepted, easy to apply, widely used

models for environmental transport. Moreover, realistic models of environmental transport are usually extremely complex, and it is impracticable to use them in priority-setting exercises.

Persistence. Chemicals can be transformed and degraded in the environment through chemical, photochemical, or microbial processes. The relative importance of these processes will be influenced by the compartment of the environment with which we are primarily concerned. Reactions leading to simpler compounds which are part of a series leading ultimately to the free elements or elemental oxides are considered to represent "degradation," Other reactions lead to ''secondary pollutants.

Persistent chemicals are often given priority over easily degraded or transformed chemicals in hazard assessment systems, on the assumption that persistent chemicals are more likely to spread through the environment and will continue to accumulate as long as they are released. When persistence is used as a criterion for hazard assessment, it is important to be aware, however, that there are cases in which degradation products or secondary pollutants are more toxic than the chemical substances initially released,

Biodegradability. Although all living things can play a role in transformation of chemicals in the environment, the lead role is attributed to micro-organisms. The role of micro-organisms in transforming chemicals is extremely important in the lithosphere and also important in the hydrosphere. Micro-organisms are frequently efficient at metabolizing natural chemicals in their environment. Industrial chemicals are inherently less likely to be rapidly degraded by micro-organisms. Parameters often used as indices of biodegradability are the biochemical oxygen demand (BOD) or chemical oxygen demand (COD), Estimates of biodegradability can sometimes be based on chemical structure.

Chemical reactivity. The assessment of the chemical reactivity of a compound is often based on known physical and chemical properties such as:

- physical state,
- vapor pressure,
- solubilities,
- auto-oxidation propensity,
- redox potential,
- acid-base characteristics,
- rate of hydrolysis, and
- rate of photochemical degradation.

One parameter which can-be used for persistence in the environment is half-life, the time required for removal of half of the molecules of a given compound from the environment or from a specific compartment of the environment. Half-life in the atmosphere, for example, would be a function of such properties as photoreactivity, reactivity towards active forms of oxygen, water volubility, volatility, and adsorption to fine particulate.

Bioaccumulation. Bioaccumulation can be defined as the long-term presence of a xenobiotic substance in living tissue at concentrations significantly higher than those in the surrounding environment. Chemicals that bioaccumulate are often given priority over other chemicals in hazard-assessment schemes. Concentrations of chemicals that bioaccumulate are likely to increase along a food chain, a process referred to as "biomagnification. " For such chemicals, residue levels tend to be higher in herbivorous animals than in plants, higher in carnivorous animals than in herbivores, and highest in carnivores that eat other carnivores. Since humans may eat organisms in any of these categories and since chemicals which bioaccumulate will usually be stored in human tissues, if such chemicals have any toxic properties they may pose a higher risk to human health than would be predicted on the basis of environmental concentrations alone.

Since bioaccumulation is often associated with a high lipid volubility relative to water volubility, the partition coefficient can be used as an indicator of the tendency to bioaccumulate. The partition coefficient is a measure of the distribution of a solute between two immiscible liquid phases in which it is soluble. For a single molecular species, the partition coefficient is a constant and does not depend on relative volumes of solutions used. The most commonly used coefficient indicates relative volubility in organic and aqueous phases, providing information on the hydrophobic or hydrophilic nature of the compound.

Although absorption and accumulation of toxic pollutants are related to their partition coefficients, partition coefficient alone does not determine bioaccumulation. Other characteristics of the chemical (reactivity, vapor pressure) and of the organism (metabolic pathways, nutritional status, fat content of body tissue) will also influence the extent of bioaccumulation. Active accumulation of a substance that resembles another chemical is frequently predictable from the properties and structures of both,

For inorganic compounds relative volubility is not the primary factor in determining extent of storage in body tissues. Passive accumulation

through formation of complexes with organic ligands, especially those containing sulfhydryl and amine groups, can also occur. The synthetic compounds most likely to accumulate in this way are organometallic chemicals. The tendency of a chemical to accumulate in this way can be predicted from knowledge of the likelihood of the chemical to form complexes with natural bases.

Population at risk. The size or type of population exposed may be considered as a factor in setting priorities for toxic chemicals. Types of populations at risk could be:

- the general human population,
- population of a geographical region,
- population of a specific neighborhood,
- population in the immediate vicinity of an industrial plant,
- people whose diets contain a high amount of particular foods,
- occupational groups, and
- highly susceptible groups.

Population groups can be further classified according to whether their exposure is voluntary or involuntary. Priority considerations should be given to chemicals to which there is extensive involuntary public exposure or to which susceptible segments of the population are exposed. Some ranking schemes consider certain segments of the population more ‘‘valuable’ than others (e.g., the young more “valuable" than the old). This approach is highly subjective and ethically questionable.

## Toxicity

The toxicity of a chemical is the second determinant of hazard. The difficulties encountered in estimating the biological activity of a chemical are as severe as those encountered in estimating exposure. Here we find ourselves at ‘‘the frontiers of scientific knowledge” in attempting to evaluate the significance of laboratory data for human experience.

Most priority-setting efforts have scored chemicals on a series of toxic effects, There are, however, some general indices of toxicity, such as the threshold limit values for atmospheric exposure in the workplace established by the U.S. Department of Labor and the American Council of Governmental and Industrial Hygienists, tolerance levels for pesticides in food set by EPA, or “action levels’” for food contaminants set by FDA. These indices are based on reviews of a range of toxicity data and represent attempts to identify threshold levels for hazard or for lack of assurance of safety. Although the reliability of such indices as precise measures of degrees of hazard is debatable, where available they are useful in priority-setting exercises because they represent an attempt to weigh all toxicity data available at the time when they were established.

Metabolic factors.

1. Uptake and absorption.—Even if the amounts to which people ‘may be exposed could be determined, we still would not know the amount that could be expected to enter the human body and cause biological damages. The term “penetrability” is sometimes used to represent that portion of the chemical to which the person is exposed that is expected to be absorbed into the body, This factor includes consideration of both the routes of exposure and the fraction of the chemical absorbed after exposure by each route,
2. Biotransformation. -The metabolic conversion of a chemical within the human body should be considered, as far as possible, in assessing potential health effects. A chemical can be detoxified, activated, or converted to a compound with different biological properties. The metabolic pathway can be dose-dependent.
3. Elimination. —The turnover rate in the human body can be an important factor in assessing biological effects. If, however, a chemical has been scored for bioaccumulation as an exposure factor, it may not be necessary for it to be scored for turnover in humans, as these factors are closely related,

Absorption, bioconversion, and elimination are complex factors and are difficult to handle for ranking purposes, Information is not readily available and is rarely compiled in easy-to-use secondary sources. For many chemicals, no metabolic information is available. When metabolic studies are found, they are often reported in qualitative rather than quantitative form. Relating metabolic information to adverse health effects often requires a high level of expertise in toxicology. Despite all these problems, a toxicological ranking system which takes into account these metabolic factors is more sophisticated than and usually superior to a system which does not,

Acute toxicity. The biological effect of a chemical depends on the quantity of the chemical with which the organism must deal, Chemicals having adverse effects at low dosage would be considered more toxic than chemicals having similar effects only at much higher dose levels. It is difficult to perform this ranking at low effect levels. The

effects of low dosages are often subtle. Direct experimental estimation of the level affecting 1 percent of the population may require several hundred animals to obtain adequate statistical precision. For these reasons, lethal dosage levels are usually used in ranking chemicals for acute toxicity.

A common parameter of acute toxicity is the $LD_{50}$, the dose of a substance at which half the test animals would die. To be comparable, results should be based on animals of the same species, strain, sex, and age. The same route of administ ration should be used.

Other commonly used parameters of acute toxicity based on lethal doses are:

$LC_{50}$ = the concentration which is lethal to half the test population. The duration of exposure should be specified. LC is usually used for concentration in air, but can also be used for concentration in the ambient water to which aquatic organisms are exposed

$LD_{L,,}$ = the lowest reported lethal dose

$LC_{L0}$ = the lowest reported lethal concentration

Available data on these parameters for **16,500** different chemicals are summarized in the *Registry of Toxic Effects of Chemical Substances* published by NIOSH. The major objection to acute lethality as a basis for ranking environmental contaminants is that the acute lethal doses are very much higher than those levels one would expect to find in the environment. Furthermore, values for acute lethality can vary widely between species. Use of this parameter can be justified, however, on the basis that the $LD_{50}$ is at least a crude index of biological activity. It is reasonable to consider a chemical w i t h a very low $LD_{50}$ to be a relatively toxic chemical. on the other hand, a chemical with a high $LD_{50}$ is not necessarily safe, since long-term exposure a t low concentrations may have such adverse effects as carcinogenicity or damage to the reproductive system.

Data on acute toxic effects other than lethality are less frequently compiled, are more difficult to use for ranking purposes since they arc not usually reported in numerical form, and may not be indicative of effects occurring at the low dosage levels ordinarily found in the environment. Nevertheless, nonlethal acute effects can provide useful information about target organs and should be considered as part of the overall picture when subjective judgments are made.

Carcinogenicity. In principle, it would be useful to categorize chemicals as strongly carcinogenic, moderately carcinogenic, weakly carcinogenic, co-carcinogenic, or having no neoplastic effects. There is usually not enough information available, however, to do this. Dose-response curves are rarely determined for carcinogens. Negative results in carcinogenicity tests are usually not accepted as proof of noncarcinogenicity. Comparisons between carcinogenic "potency' of various chemicals have been made on the basis of percent age of a test population developing malignant tumors, the number or types of species in which positive results have been reported, the types of tumors observed, the lowest dosage causing malignancy, or the lag time between administration of chemical and observation of tumors.

Chemicals are sometimes classified with respect to the degree of certainty of their carcinogenicity (e. g., known carcinogen or suspected carcinogen). EPA has recently attempted to order the NIOSH list of suspected carcinogens according to the relative degree of concern that might be warranted regarding possible human carcinogenic potential. A four-digit code was used. The first digit represented the species in which carcinogenic response was reported. The second digit designated the number of different species for which a carcinogenic response was reported. The third digit was assigned on the basis of route of administration. The last digit was a count of the number of different species-route combinations.

The most complete source of data and references related to chemical carcinogenesis is the Public Health Service's Survey of *Compounds Which Have Been Tested for Carcinogenic Activity.* A master index of the series is maintained on tape at the National Cancer Institute headquarters.

Evaluations of carcinogenic risk are made by the International Agency for Research on Cancer under the auspices of the World Health Organization. They do not use a formal ranking system.

Mutagenicity, A mutation is defined as any heritable change in genetic material. The results of mutations are usually undesirable and may include abortion, congenital anomaly, genetic disease, lowered resistance to disease, decreased lifespan, infertility, mental retardation, senility, or cancer.

The reliability and accuracy of the prediction of mutagenicity in man from the ability of a chemical to produce mutations in experimental tests systems is controversial. Many types of tests are currently available for use as indicators of mutagenic potential. Some (e. g., the Ames test, the dominant lethal test) are actual tests for mutage-

nicity. Others test for a variety of events relating to, or at least correlated with, mutagenesis. Some such tests are for chromosome aberrations, DNA damage or repair, increased rate of sister chromatid exchange, or other phenomena considered to be relevant to mutagenic potential. Because even those tests that actually demonstrate mutagenicity are highly specific for detecting a single type of mutation, results of a battery of tests are desirable for an evaluation of mutagenic potential of a chemical substance,

Structure-activity relationships have met with limited success in prediction of mutagenicity. Many chemical mutagens (but not all) act as electrophiles permitting a prediction of mutagenic potential of compounds that might form a reactive electrophilic species.

Many difficulties are encountered in extrapolating to man results obtained in microbial, mammalian cell culture, or test animal systems. Potential for mutagenic effects in man should be assessed only after results of testing in various experimental systems are considered in conjunction with other relevant factors such as chemical structure, biochemical activity, and metabolism in man.

Teratogenicity. Certain chemicals, when administered to a pregnant female, can interfere at a critical stage of embryogenesis or organogenesis and can cause embryonic death or malformation, A chemical with such properties is a teratogen. Testing for teratogenicity should ideally involve administration of the test substance only at the period critical for organogenesis of the system sensitive to the teratogen. Sensitive periods of organogenesis are characteristic of particular chemical teratogens.

At the present time, only tests in pregnant mammals are generally accepted by scientists and regulatory agencies as valid tests for teratogenicity, because the maternal-placental embryonic relationship cannot be duplicated in submammalian test systems. Other test systems sometimes used as indicators of teratogenic potential include bacteria and other unicellular organisms, somatic cells in culture, tissue culture, organ culture, intact invertebrate embryos, cultured mammalian embryos, and incubating chick embryos. Of these systems, chicks and to a lesser extent fish are the most widely used,

It is difficult to rank chemicals on the basis of teratogenic potency. The type of dose-response data needed for quantification of teratogenic risk is seldom available. Interspecies extrapolation is poorly understood. There is an enormous range of variability of teratological end points. Chemical structure has been found to be of little use in predicting teratogenicity.

Other toxic effects.

1, Effects observed in humans, —Reports of toxic effects in humans can be based on epidemiological or clinical observations. There are severe problems in interpreting this type of information. Humans are rarely exposed to only a single chemical substance, It is usually difficult to find control groups with zero exposure to an environmental contaminant. Results based on occupational exposure may underestimate risk, because susceptible segments of the population (infants, children, the aged, the chronically ill) are excluded from the workplace. When workers become sick they often stop working and are no longer part of the occupational cohort. Another problem in interpreting human data is that the doses are often unknown.

2. Chronic toxicity, —Biological effects of a chemical administered in low doses over an extended period of time may be quite different from acute effects. Chronic exposure test protocols are more relevant than are acute protocols to the types of exposure due to environmental contaminants.

Because of the wide range of end points observed during chronic exposure tests, comparisons are difficult to make. Comparing one type of effect with another (for example, comparing impaired fertility with liver damage) on the basis of severity is highly subjective. Ranking chemicals on the basis of chronic toxicity therefore requires a high level of scientific expertise.