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EVALUATION OF ENVIRONMENTAL CARCINOGENS

REPORT TO THE SURGEON GENERAL, USPHS
APRIL 22, 1970

AD HOC COMMITTEE ON THE EVALUATION OF LOW LEVELS
OF ENVIRONMENTAL CHEMICAL CARCINOGENS

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"FEDERAL ENVIRONMENTAL PESTICIDE CONTROL ACT"

Hearings before the Subcommittee on Agricultural Research and General Legislation of the Committee on Agriculture and Forestry, United States Senate, March 23, 24, 25, and 26, 1971; pages 677-697.

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INTRODUCTION

Establishment of this Ad Hoc Committee was requested on October 24, 1969, by the Deputy Assistant Secretary for Health and Scientific Affairs.

The task of the Committee is to review the problems relating to the evaluation of low levels of environmental chemical carcinogens, to consider the scientific bases on which such evaluations can be made, and to advise the Department of HEW on the implications of such evaluations.

The Committee, in addressing itself to the problems of environmental exposures to chemical agents from all sources, has considered the scientific criteria for evaluation of carcinogenic hazards.

Many previous recommendations on the criteria to be used for evaluating environmental chemical carcinogenic hazards have been made for specific sources of exposure or for specific groups of substances (e.g. food additives, pesticides, certain occupational carcinogens). In some cases this approach has led to an uneven assessment of risks from different sources and to an uneven approach to preventive measures.

The task of this Committee covers a broader area and includes an appraisal of the scientific criteria for evaluation of chemical carcinogenesis hazards in the total environment.

I. RECOMMENDATIONS

In full consideration of the past and present states of carcinogenesis investigation this Committee offers the following recommendations:

1.a. Any substance which is shown conclusively to cause tumors in animals should be considered carcinogenic and therefore a potential cancer hazard for man. Exceptions should be considered only where the carcinogenic effect is clearly shown to result from physical, rather than chemical, induction, or where the route of administration is shown to be grossly inappropriate in terms of conceivable human exposure.

b. Data on carcinogenic effects in man are only acceptable when they represent critically evaluated results of adequately conducted epidemiologic studies.

2. No level of exposure to a chemical carcinogen should be considered toxicologically insignificant for man. For carcinogenic agents a "safe level for man" cannot be established by application of our present knowledge. The concept of "socially acceptable risk" represents a more realistic notion.

3. The statement made in 1969 by the Food Protection Committee, National Research Council (see Appendix II) that natural or synthetic substances can be considered safe without undergoing biological assay should be recognized as scientifically unacceptable.

4. No chemical substance should be assumed safe for human consumption without proper negative lifetime biological assays of adequate size. The minimum requirements for carcinogenesis bioassays should provide for: adequate numbers of animals of at least two species and both sexes with adequate controls, subjected for their lifetime to the administration of a suitable dose range, including the highest tolerated dose, of the test material by routes of administration that include those by which man is exposed. Adequate documentation of the test conditions and pathologic standards employed are essential.

5. Evidence of negative results, under the conditions of the test used, should be considered superseded by positive findings in other tests. Evidence of positive results should remain definitive, unless and until new evidence conclusively proves that the prior results were not causally related to the exposure.

6. The implication of potential carcinogenicity should be drawn both from tests resulting in the induction of benign tumors and those resulting in tumors which are more obviously malignant.

7. The principle of a zero tolerance for carcinogenic exposures should be retained in all areas of legislation presently covered by it and should be extended to cover other exposures as well. Only in the cases where contamination of an environmental source by a carcinogen has been proven to be unavoidable should exception be made to the principle of zero tolerance. Exceptions should be made only after the most extraordinary justification, including extensive documentation of chemical and biological analyses and a specific statement of the estimated risk for man, are presented. All efforts should be made to reduce the level of contamination to the minimum. Periodic review of the degree of contamination and the estimated risk should be made mandatory.

8. A basic distinction should be made between intentional and unintentional exposures.

a. No substance developed primarily for uses involving exposure to man should be allowed for wide-spread human intake without having been properly tested for carcinogenicity and found negative.

b. Any substance developed for use not primarily involving exposure in man but nevertheless resulting in such exposure, if found to be carcinogenic, should be either prevented from entering the environment or, if it already exists in the environment, progressively eliminated.

9. A system should be established for ensuring that bioassay operations providing data upon which regulatory decisions are made be monitored so that their results are obtained in accordance with scientifically acceptable standards.

10. A unified approach to the assessment and prevention of carcinogenesis risks should be developed in the federal legislation; it should deal with all sources of human exposure to carcinogenic hazards.

11. Clear channels should be identified for the regulatory function of different Government departments and agencies in the field of cancer prevention. Establishment of a surveillance and information program would alert all concerned Government agencies to the extent and development of information on formation on carcinogenic hazards.

12. An ad hoc committee of experts should be charged with the task of recommending methodos for extrapolating dose-response bioassay data to the low response region (1-10000% to 1-10000000%). The low doses corresponding to the responses in this range are the ones which have direct relevance to the human situation.

II. BACKGROUND

Knowledge of cancer causation by chemicals originates from clinical observations, going back as far as 1775 with Pott's discovery of soot as the causative agent in chimney sweeps' cancer. Several major classes of carcinogenic agents were first discovered by their effects on man. Experimental animal models for the determination of the potential carcinogenic activity of chemicals were only developed in the last 50 years, and most of them have been studied only in the last 20 years.

The effects of carcinagens on tissues appear irreversible. Exposure to small doses of a carcinogen over a period of time results in a summation or potentiation of effects. The fundamental characteristic which distinguishes the carcinogenic effect from other toxic effects is that the tissues affected do not seem to return to their normal condition. This summation of effects in time and the long interval (latent period) which passes after tumor induction before the tumor becomes clinically manifest demonstrate that cancer can develop in man and in animals long after the causative agent has been in contact and disappeared.

It is, therefore, important to realize that incidences of cancer in man today reflect exposure of 15 or more years ago; similarly, any increase of carcinogenic contaminants in man's environment today will reveal its carcinogenic effect some 15 or more years from now. For this reason it is urgent that every effort be made to detect and control sources of carcinogenic contamination of the environment well before damaging effects become evident in man. Similar concepts may apply to the needs for evaluation of other chronic toxicity hazards. Environmental cancer remains one of the major disease problems of modern man.

An agent which is causally related to the occurrence of cancer in man or animals is defined as a carcinogen or oncogen. The number of known carcinogenic agents includes several groups of viruses, various physical factors, and hundreds of chemicals.

Viruses of different types are known to induce cancer in animals; none has yet been proven to evoke cancer in man. If specific viruses are proven to be causally

related to cancer induction in man, the frequency of certain human tumors might be reduced in the future by immunization procedures.

Physical factors are known to cause cancers in man and animals. For example, ultraviolet radiation causes skin cancer, and ionizing radiation cancer of various organs (e.g. leukemias, lung cancer, bone sarcomas, skin cancer). Exposure to a "background level" has been widely considered as unavoidable and, in the case of ultraviolet light, even necessary as an integral part of our natural environment. Strong epidemiologic and experimental evidence indicates the existence of a direct dose-response relationship between exposure to radiation and carcinogenic effects. Tolerance levels have been suggested for various forms of radiation and health benefits have been realized from their application. Evaluation of radiation hazards has been approached through measurement of the total cumulative dose of radiation exposure. Some carcinogenic radiation hazards, such as certain occupational exposures (e.g. radiation in uranium mines), are still not effectively controlled.

Chemicals of many classes produce cancer in a large number of organ sites in animals. Cancers in man are known to be caused by several individual chemicals and by materials composed of mixtures of chemicals. Chemical carcinogens have been shown to act by surface contact with skin or mucosae, by inhalation, by ingestion, and occasionally by injection or implantation (medical or accidental). Chemicals may induce cancer at the site of initial contact (e.g. skin cancer from radionuclides), the site of metabolism and detoxification (e.g. liver or kidney cancer from aflatoxin or nitrosamines), or the site of excretion (e.g. urinary polynuclear hydrocarbons), the site of selective localization (e.g. bone cancer bladder cancer from aromatic amines). A complex and often uneven approach to the problem of preventing exposure to chemical carcinogens has developed over the years. It has become increasingly obvious that the hazard from a single chemical carcinogen cannot be evaluated out of context of the total environmental exposure (1). Estimation of the "cumulative carcinogenic dose" resulting from all possible chemical carcinogens or even from all sources of a single type or class of chemical carcinogens is presently impossible.

Prevention of exposure to known carcinogenic chemicals depends largely on man's ability to control their entry into the environment. Certain chemical carcinogens are natural products (e.g. metabolites of the amino acid tryptophan) or naturally occurring contaminants (e.g. mycotoxins). Others are formed in the processing of natural products. Many, such as polynuclear hydrocarbons (e.g. benzo[a]pyrene), occur almost ubiquitously in our modern industrialized environment. They derive from most sources of organic combustion. A class of very potent carcinogens discovered only in recent years, the N-nitrosamines, include compounds that may be formed in the environment from nitrites and secondary amines. Many other known chemical carcinogens have been introduced as synthetic materials or by-products into man's present environment through a wide range of newly-developed industrial processes. Some of these, such as food additives, medicinal products, cosmetics, and certain household products or pesticides, were developed for human use. Several carcinogens derive from products such as tobacco smoke, developed exclusively for human use. In other cases chemical carcinogens not intended primarily for human exposure are introduced into the general environment and eventually come in contact with its inhabitants; many substances (certain polynuclear hydrocarbons, pesticides, metals, dusts, and fumes, etc.) gain widespread environmental distribution, thereby becoming pollutants of the air, soil, water, and food. Prevention of exposure to this broad spectrum of chemical carcinogens must take a variety of forms.

The production of chemicals recognized as carcinogens for uses involving intentional human exposure can be identified and effectively eliminated. Exceptions to this approach should be made for substances that involve a well-defined health benefit (e.g. certain chemotherapeutic drugs). Use of such substances should be accepted on the basis of extraordinary evidence that their health benefit outweighs their risk.

The production of specific carcinogenic chemicals for uses that do not primarily involve an intentional exposure of man, but which result in such environmental contamination that extensive human exposure becomes inevitable, must also be controlled. The most effective prevention of exposure in man is the elimination of carcinogen production, or control of entry into the environment.

A large group of chemical carcinogens (e.g. combustion products, mycotoxins, and other natural products) is widely disseminated in the environment from sources that can only be partly controlled. For these contaminants, as

well as for products which have been widely spread in the environment before their carcinogenicity was recognized, the only possible approach to exposure reduction is to monitor their environmental distribution and subsequently minimize their contact with humans.

Modifying factors are known to condition the development of neoplasia in man and animals. They can act intrinsically or extrinsically (e.g. hormonal imbalances, metabolic characteristics or abnormalities, caloric intake, dietary factors). Understanding of their specific effects in man, however, is still not adequate to serve as a reliable basis for preventative action.

Interactions among multiple factors have received limited attention to date. There are well-documented instances in animal studies of strong synergistic effects produced by chemicals in combination with radiation, viruses, or other chemicals. The epidemiological patterns of certain human cancers implicate combined effects of multiple agents (e.g. inhalation of radon and radon daughters in uranium mines and cigarette smoking).

The types of cancer in man that are due, directly or indirectly, to extrinsic factors are thought to account for a large percentage of the total cancer incidence (2). These include tumors of the skin, the respiratory, gastrointestinal and urinary tracts, hormone-dependent organs (such as the breast, thyroid, and uterus), and the hemopoietic system. During the past decade considerable progress has been made in the detection of carcinogenic agents and the analysis of their biological effects. New approaches to the interpretation of quantitative relationships between exposures and carcinogenic effects in man and animals are being developed. It is estimated, therefore, that the majority of human cancers are potentially preventable (2).

III. ANIMAL BIOASSAY RESULTS AND EVALUATION OF RISKS IN MAN

In order to evaluate the hazard of a chemical for man, one must extrapolate from the animal evidence. It is essential to recognize that no level of exposure to a carcinogenic substance, however low it may be, can be established to be a "safe level" for man. This concept, put forward in the 1950's, remains true in 1970. The current legislation in the field of food additives, with its "anticancer clause", is based on this principle (Federal Food, Drug and Cosmetic Act, as amended, Sect. 409 (c) (3) (A)).

The reasons for retaining this "anticancer clause" were effectively summarized in 1960 by Secretary of Health, Education and Welfare Arthur S. Flemming in testimony to Congress (3) on the subject of extending the clause to cover the use of food colors, with the following statement.

"The rallying point against the anticancer provision is the catch phrase that it takes away the scientist's right to exercise judgment. The issue thus made is a false one, because the clause allows the exercise of all the judgment that can safely be exercised on the basis of our present knowledge. The clause is grounded on the scientific fact of life that no one, at this time, can tell us how to establish for man a safe tolerance for a cancer-producing agent.

"Until cancer research makes a breakthrough at this point, there simply is no specific basis on which judgment or discretion could be exercised in tolerating a small amount of a known carcinogenic color on food additive.

"As I pointed out in my original testimony, the opposition to inclusion of an anticancer clause arises largely out of a misunderstanding of how this provision works. It allows the Department and its scientific people full discretion and judgment in deciding whether a substance has been shown to produce cancer when added to the diet of test animals. But once this decision is made, the limits of judgment have been reached and there is no reliable basis on which discretion could be exercised in determining a safe threshold dose for the established carcinogen.

"So long as the outstanding experts in the National Cancer Institute and the Food and Drug Administration tell us that they do not know how to establish with any assurance at all a safe dose in man's food for a cancer-producing substance, the principle in the anticancer clause is sound.

"I want to emphasize the statement I made on January 26 that the Food, Drug, and Cosmetic Act, as it now stands, will be enforced to prohibit the addition of cancer-producing substances to food unless a law should be passed directing us to follow another course of action.

"~~Even though we have this authority in the law, we urge the Congress to~~

"Even though we have this authority in the law, we urge the Congress to

join with the executive branch to give added assurance to the consuming public by directing the anticancer clause in the proposed color additives amendment.

"Again, we say, however, that we believe the issue is so important that the elected Representatives of the people should have the opportunity of examining the evidence and determining whether or not the authority should be granted."

The scientific basis on which the Government's position was established in 1960 remains valid. The progress of knowledge in carcinogenesis in the last decades has only strengthened the points made in Secretary Flemming's testimony.

IV. DETECTION OF LOW LEVELS OF CARCINOGENS IN THE ENVIRONMENT

To establish the presence of "low levels of carcinogen in the environment" requires that 1) the presence of the material in question be recognized in the environment and 2) the material be recognized as carcinogenic. To evaluate the impact of a chemical in the human environment, it is useful to prepare an "environmental profile" to reflect the distribution of this material in time and space. Failure to detect the presence of a compound implies only that the compound is present, if at all, in concentrations below the detectable limit of the analytical method used. These "sub-detection levels" cannot be differentiated from "zero". From the distribution profile and additional information on the conditions of uptake in man the approximate level and extent of exposure for population segments can be estimated.

In recognizing a chemical as a carcinogen, the limiting factor is the sensitivity and specificity of the bioassay system used. A bioassay system designed to detect tumor induction only at or above a given level under the conditions of the test (e.g. a 25% incidence of a specific tumor type) will fail to reveal carcinogenicity below that level. Compounds whose carcinogenic effects fall below specific bioassay detection limits must not be considered innocuous. Such materials must be characterized as presenting a carcinogenic risk no greater than that defined by this lower limit.

Methodology for the determination of chemical contamination in the environment and of biological activity of carcinogens are discussed in the following sections.

A. Chemical Detection Methods

Methods for detection of low levels of carcinogens in the environment have increased in accuracy and reliability over the past several years. The lower limits of detection for different types of known carcinogenic substances are extremely variable, extending over several orders of magnitude from very sensitive methods (e.g. 1 part per billion of benzo(*a*)pyrene or aflatoxin) to rather insensitive ones (e.g. for aromatic amines). In principle, analytical methods should be capable of detecting carcinogenic materials at any level or in any condition which has relevance to human exposure. For this reason, increasingly sensitive analytical techniques are needed, and indeed many have been developed over the last 10 years. Appendix I summarizes the present state of the art in the analytical determination of low levels of environmental carcinogens (*1*) and indicates the lower limits of detection available today, in contrast with those of 1959. Much of the improvement in methodology is attributable to the application of gas-liquid chromatographic techniques. Within the next few years sizable additional improvements in the sensitivity of analytical methods are likely to be achieved.

It is important to consider how widely the new analytical methods can be applied for the detection of a given carcinogenic contaminant in different materials. While highly sensitive analytical methods can be devised to detect a chemical in specific materials, these same methods might be powerless in the analysis of the same chemical from other source materials (e.g. dimethylnitrosamine can be detected in the alcoholic beverages at 1 ppb, but in foods only at 10–100 ppb). An uneven evaluation of the sources of environmental contamination may result. Development of widely applicable procedures will provide a more balanced evaluation of environmental contamination.

B. Biological Detection Methods

The carcinogenic activity of materials can only be detected by long-term biological tests. At the present time the chemical structure or physico-chemical properties of a compound do not provide a reliable basis for prediction of freedom from carcinogenic activity. Several structure-activity correlations are valuable indicators of the possible carcinogenicity of a compound, but none can be

used to classify the compound as non-carcinogenic. Short-term bioassays that determine the effect of certain chemicals on selected biologic targets have not been reliable for prediction of carcinogenic activity.

The present state of the art requires long-term bioassays in mammalian species for the experimental identification of carcinogenic activity. United States law requires that food additives and various other materials be tested in animals by the intended route of human exposure. Similar tests have not been required for some materials to which humans are exposed by other than the oral route. The expanding production and use of chemicals in household products results in extensive human exposure (via the skin and respiratory tract) to dusts and aerosols; little information is available on the chronic toxicity of these materials by these routes of administration. It would not be wise to wait for the results of these "experiments in man" before instituting animal experimentation.

Bioassays are always performed on a number of animals which is extremely small when compared with the millions of humans exposed to most environmental carcinogens. Such studies can only detect carcinogenic effects resulting in fairly high incidences. For example, an observed outcome of no tumors in a test group of 100 animals, as well as in 100 negative controls, only provides assurance, at the 99 percent probability level, that the true tumor risk is under 4.5 percent. The maximum probable risk is 0.46 percent if groups of 1000 animals are used. It would require tumor-free results in 450 animals to establish with like probability that the risk is under 1 percent (4).

The assessment of the carcinogenic activity of a chemical depends on a variety of parameters. These include not only the total number of tumors induced but also their multiplicity, latent period, morphologic type, and degree of malignancy. The induction of tumors diagnosed as benign as a result of treatments has been interpreted by certain groups in the past as not sufficient to demonstrate a "carcinogenic" effect. This is a dangerous position since few, if any, substances are known to have produced only benign tumors and no malignant ones when properly and repeatedly tested. This has been pointed out in the Report of the Subcommittee on Carcinogenesis of the FDA Committee on Protocols for Safety Evaluation (5).

The important scientific problem of defining the sensitivity of a bioassay system used for testing materials of unknown activity has received insufficient attention. The interpretation of both positive and negative findings is strictly dependent on such definition as well as on the results obtained in negative, vehicle, positive and colony control animals. A bioassay result is meaningful only when accompanied by a statement of the sensitivity and specificity of the bioassay design used. An observed incidence of a given tumor type in a test group has no meaning without adequate information on the appropriate controls. Far too little work has been done using adequate positive controls. Lack of tumor response in a given experimental system cannot be interpreted as negative evidence if positive controls also yield negative results or if no positive controls have been included to show that the experimental system used is appropriate.

A body of knowledge has developed over the years on the response of experimental animals to chemical carcinogens. Several committees of experts in the field of carcinogenesis convened by national and international bodies over the past 15 years have formulated general principles for performance and evaluation of carcinogenesis studies in animals. The recommendations put forth by these committees have shown remarkable unanimity (2, 5–10) and are widely accepted in principle by the scientific community (11–13). General requirements for testing procedures, which have been outlined by these groups, include specification of criteria for the following:

1. selection of materials to be tested;
2. chemical and physical characterization of the test materials;
3. selection of appropriate animal species and group size; and
4. choice of appropriate routes and levels of administration.

In addition, recommendations concerning the lifetime maintenance and pathological examination of experimental animals have been outlined.

Two principles are recognized as fundamental to the evaluation of carcinogenesis bioassays.

1. The minimum requirements for carcinogenesis bioassay should include adequate numbers of animals of at least two species and both sexes with adequate positive and negative controls, subjected for their lifetime to the

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administration by appropriate routes of a suitable dose range of the test material, including doses considerably higher than those anticipated for human exposure.

2. Any substance which is shown conclusively to produce tumors in animals, when tested under these conditions, should be considered potentially carcinogenic for man.

V. QUANTITATIVE RELATIONSHIPS

The major new argument presented today against the "anticancer clause" is that the marked increase in sensitivity of many analytical methods makes it possible to detect low levels of carcinogens in a broader segment of the environment and that, therefore, the immediate enforcement of regulations requiring a zero tolerance becomes more difficult, in some instances impossible.

New and very potent classes of chemical carcinogens, such as aflatoxin and nitrosamines, have been detected in the environment. Striking examples of potentiation in cancer induction have been reported in experimental animal tests and in epidemiologic observations. Bioassays have revealed the carcinogenicity of such widespread environmental chemicals as DDT and cyclamate, to which a large majority of the American population has been exposed.

In contrast to the analytical methods, bioassay methods have remained tools of low senitivity, capable only of detecting the highest peaks of carcinogenic activity. The factor which limits bioassay sensitivity is usually the small number of test animals used. If the bioassay design has a low probability of detecting carcinogenic effects produced by hazards at levels comparable to those present in environmental samples, then tests at such levels are wastes of time, effort and money. The need to test dose levels higher than those found in the environment is thus founded. Some substances, on the other hand, are potent carcinogens in animal test systems at levels not currently detectable in the environment. An example is provided by the recent evidence on aflatoxin. Its lowest analytically detectable level is 1 ppb. One hundred percent tumor incidence was produced in rats by a dose as low as 15 ppb. in the diet. Experiments now under way suggest that aflatoxin, when fed to rats at the lowest detectable level (1 ppb), is still carcinogenic (*16*). It has already been demonstrated to be carcinogenic at 1 ppb in the trout. These data indicate that aflatoxin may be present in food at undetectable levels and still be capable of producing cancer incidences so high as to be detectable in tests involving relatively small numbers of experimental animals.

It is impossible to establish any absolutely safe level of exposure to a carcinogen for man. The concept of "toxicologically insignificant" levels (as advanced by the Food Protection Committee of the NAS/NRC in 1969; see Appendix II), of dubious merit in any life science, has absolutely no validity in the field of carcinogenesis. Society must be willing to accept some finite risk as the price of using any carcinogenic material in whatever quantity. The best that science can do is to estimate the upper probable limit of that risk. For this reason, the concept of "safe level for man", as applied to carcinogenic agents, should be replaced by that of a "socially acceptable level of risk".

While science can provide quantitative information regarding maximum risk levels, the task ultimately selecting socially acceptable levels of human risk rests with society and its political leaders. The evaluation of the balance of benefits and risks, required for such a decision by society, should not be the result of uninformed guesswork but should be reached on the basis of complete and pertinent data, social as well as scientific. It is necessary, therefore, to define the extent in the processes of interpreting animal response data (Appendix III) and subsequently extrapolating them to man (Appendix IV). The principle of zero tolerance should be applied in all but the most extraordinary of cases.

VI. CONCLUSION

Modern society has been extremely fortunate—given the technical limits on detection of carcinogenic effects—that at least some environmental carcinogens have been identified. So-called negative data, obtained in bioassays often incapable of detecting effects below the 10 percent level, are grossly inadequate to give assurance of safety for man. Information on about 2,500 compounds tested for carcinogenic activity up through 1960 has been compiled and published (*17*). Most of these materials, however, are of no environmental significance. Data on tests reported since 1960 will be published shortly. It is estimated that data on 3,500 previously unevaluated chemicals will be included in the

forthcoming volume. It is seen, then, that about 6,000 chemicals are documented as having undergone carcinogenesis bioassay to date. Many of the referenced tests, however, were inadequate according to presently recommended standards.

If this nation wishes to identify a large segment of existing and potential carcinogenic hazards, it must institute a comprehensive program involving a concert of activities. Scientific and technical plans for the development of methodological standards should be provided by experienced agencies in collaboration with qualified advisors. It is essential that the objectivity of these advisors not be damaged by any conflicting interests.

Resources needed for the extensive bioassay screening of environmental chemicals will be considerable. In addition to the myriad of substances presently in the environment, several thousand new compounds are introduced each year. Up to 20,000 materials should be tested for carcinogenicity as a first screening of the environment. Testing 20,000 compounds by bioassay would cost about $1 billion. This estimate would increase accordingly for the more extensive testing required in less superficial evaluation. Yet even were such funds available today, they could not nearly be spent effectively. Bioassay laboratory and professional resources are just not available in quantities capable of supporting a huge testing program. A great deal of "tooling up" is prerequisite to any such expanded level of effort.

Because the latent period in human carcinogenesis is so long, epidemiologic evidence develops only over periods of 15 to 20 years. Timely decisions to exclude materials from uses involving exposure to man, therefore, must be based solely on adequately conducted animal bioassays. Retrospective human evidence of risk must not be allowed to show itself before controlling action is taken. Chemicals should be subjected to scientific scrutiny rather than given individual "rights"; they must be considered potentially guilty unless and until proven innocent. Valid evidence must come from biological assays; every bioassay report should include a statement of its limits of sensitivity. Experimental design should provide for reproducibility of test results. Since the bioassay plays such a key role in a total carcinogen control scheme, more effort must be devoted to setting standards for both the performance of tests and the interpretation of results. Only given good bioassay data can science possibly provide sound information to those who are charged with making social decisions regarding the acceptability of carcinogenesis risk levels.

An effective program to protect man from the mass of environmental cancer hazards is within reach. No more time should be allowed to pass before the recommendations set forth in this report are applied to reality.

Appendix I—Chemical Detection Methods: Analytical Procedures and Their Sensitivity

A review of these methods has recently been published by the International Union Against Cancer (*1*). A brief summary follows.

I. POLYNUCLEAR COMPOUNDS

Area of concern.—Carcinogenic materials falling into this general class are, at least potentially, produced under all circumstances where pyrolysis of organic substances occurs. Many members of this chemical group are carcinogenic. Analytical methods provide separation and determination of benza(*a*)pyrene, dibenz(*a,h*)anthracene and dibenz(*a,h*)acridine and other compounds commonly found together in combustion products (tars, soots, petroleum derivatives, etc.).

Analytical methods.—Acceptable analytical methods must be capable of separating and measuring at least the specific materials mentioned above. At present the methods which appear most effective depend on absorption, fluorescence spectrometry, mass spectrometry, or gas-liquid chromatography for quantification and one of several chromatographic techniques for separation.

Sensitivity.—The minimum concentration of polynuclear compounds which may be determined by present methods is approximately 1 part of an individual compound per billion (1959 sensitivity approximately 100 ppb.).

II. CHLORINATED HYDROCARBONS

Area of concern.—The chlorinated hydrocarbons have been and still are extensively used as industrial solvents and reactive intermediates. Carbon tetrachloride is a well-known liver toxin and is suspected of being a carcinogen. During the past decade, other chlorinated hydrocarbons have been widely used as persistent pesticides and general exposure of man has occurred. DDT, DDD, aldrin, dieldrin and heptachlor have been reported as carcinogenic in animals.

Analytical methods.—Current methods are based on extraction and condensation followed by separation and quantification by gas chromatography.

Sensitivity.—The advent of electron capture detectors has made methods of analysis for this class of compounds extremely sensitive. Cutrent minimum levels of detection are about 0.1 ppb (1959 sensitivity approximately 10 ppb).

III. AROMATIC AMINES AND CHEMICALLY RELATED COMPOUNDS

Area of concern.—For purposes of this discussion the "aromatic amine" are considered to include not only the substituted aromatic amines but also those compounds (nitro-, azo-, or hydroxylamine compounds) capable of being converted into aromatic amines by metabolic processes. Occupational exposure and exposure through the air, foodstuffs, plastics, and drinking water pose threats of carcinogenic hazards for humans. One must also consider the contribution to the carcinogenic load of endogenous aromatic amines such as certain tryptophan metabolites.

Analytical methods.—General methods for the determination of "total aromatic amines" are of little value because of the wide variation in carcinogenicity between members of the class. Estimation of specific substances is generally effected by their conversion to primary aromatic amines and then to azo dyes by diazotization and coupling; the azo dyes are separated chromatographically and estimated colorimetrically.

Sensitivity.—Methods for detection of members of this general class vary widely in their ensitivity due to the diverse properties of the compounds included. Azo compounds are easily estimated at sensitivities on the order of 10–100 ppb, while aromatic amines and hydroxylamine can be estimated with precision only at levels of about 1 ppm (1959 sensitivity about the same).

IV. N-NITROSO COMPOUNDS

Area of concern.—During recent years many members of this class of chemicals (nitrosamines and nitrosamides) have been recognized as highly potent carcinogens capable of inducing cancer in a variety of organ sites. There is a growing concern that these materials may represent significant cancer hazards to man. These compounds first came to our attention as a result of their utilization as industrial solvents and chemical intermediate, but they may be widely distributed at low levels in a variety of natural products. It is suspected that they may even be formed by the interaction of natural products in the organism or during food preparation.

Analytical methods.—Methods in current use depend on the extraction of these substances from a variety of starting materials and cleanup of the extract by various chromatographic techniques followed by quantification of the individual compounds by gas-liquid chromatography. Specific methods have only been developed for a few individual members of the class. No satisfactory methods for the measurement of nonvolatile nitroso compounds have yet been developed.

Sensitivity.—Minimum detectable levels for the individual compounds are at present about 100 ppb (1959 sensitivity=relatively insensitive colorimetric or polargraphic procedures).

V. AFLATOXINS

Area of concern.—Human exposure to the aflatoxins occurs principally by way of contaminated foods. It is now clear that such contamination can occur in essentially any food commodity, when harvest, storage, or transport conditions permit the growth of specific spoilage molds.

Analytical methods.—Currently used methods involve extraction and cleanup followed by identification of the compounds on thin layer chromatograms viewed under long wave ultraviolet light.

Sensitivity.—Although problems are associated with all of the presently available techniques, detection is possible at the level of 1 ppb (1959 sensitivity=problem was unrecognized).

VI. INORGANIC SUBSTANCES

Area of concern.—A number of inorganic substances of common occurrence in the environment have been reported in the past to be carcinogenic in man or certain animal species. They include compounds containing the following elements: arsenic, beryllium, cadmium, chromium, cobalt, lead, nickel, silver, titanium.

Analytical methods.—Analysis of the metals is performed today by atomic absorption spectroscopy after apropriate extraction and concentration procedures.

Sensitivity.—The lower limits of detection for the metals listed are on the order of 1 ppb (1959 sensitivity=about 10 ppb).

VII. ASBESTOS

Area of concern.—This substance is a fibrous particulate material produced in vast amounts for many industrial uses and recently found to be a widespread air pollutant. Major monitoring needs concern its presence in the general atmosphere and as an industrial dust.

Analytical methods.—Although sensitive methods are available for the detection of the elemental components of this substance, no specific chemical methods for identification of asbestos itself are available. Its estimation is still based on microscopic identification and count of asbestos particles in measured samples.

Sensitivity.—Extremely low and little improved since 1959.

VIII. OTHERS

A number of other carcinogens, belonging to a wide variety of chemical classes, need to be analyzed with specific methods. Their enumeration exceeds the limits of the present discussion. It is also necessary to improve the detection of materials which are recognized as potential sources of carcinogens and for which no adequate analytical methods are presently available (e.g. secondary amines and nitrites, which may interact to form nitrosamines).

APPENDIX II—COMMENTS ON 1969 REPORT OF THE FOOD PROTECTION COMMITTEE

This Committee has examined a report entitled "Guidelines for Estimating Toxicologically Insignificant Levels of Chemicals in Food" published in 1969 by the Food Protection Committee—Food and Nutrition Board of the National Academy of Sciences—National Research Council. It records its strong objections to the principles expressed in that report, which states that natural or synthetic substances can be considered safe without experimental support under certain vaguely-stated conditions.

The Food Protection Committee Report assumes that ". . . a level of insignificance may be determined if: (1) There are available adequate scientific studies that establish safe levels of similar magnitude for at least two analogous substances. (2) The acute or subacute toxicity of the new substance and two analogous substances is of the same nature and degree." For "Chemicals in Commercial Production" it recommends that: "If a chemical has been in commercial production for a substantial period, e.g. 5 years or more, without evidence of toxicological hazard incident to its production or use, if it is not a heavy metal or a compound of a heavy metal, and if it is not intended for use because of its biological activity, it is consistent with sound toxicological judgment to conclude that a level of 0.1 ppm of the chemical in the diet of man is toxicologically insignificant."

To assume (a) that a 5-year period of use has any meaning for the evaluation of chronic toxicity in man, (b) that any chemical may be considered safe simply because two "analogous substances" are "safe", and (c) that acute or subacute toxicity are reliable guidelines for evaluating long-term toxicity is to display a lack of understanding and appreciation of factors involved in chronic toxicity, particularly of the irreversible and delayed toxic effects which occur in carcinogenesis.

Since the purpose of the report is to recommend guidelines and priorities for selecting chemicals for human use without direct experimental toxicological evaluation, the lack of consideration of irreversible long-term toxic effects (which would not be ruled out by the suggested criteria) makes the suggested approach practically inapplicable and potentially dangerous.

Appendix III—A Method for Determining the Dose Compatible With Some "Acceptable" Level of Risk

(Contributed by Dr. M. A. Schneiderman)

Introduction

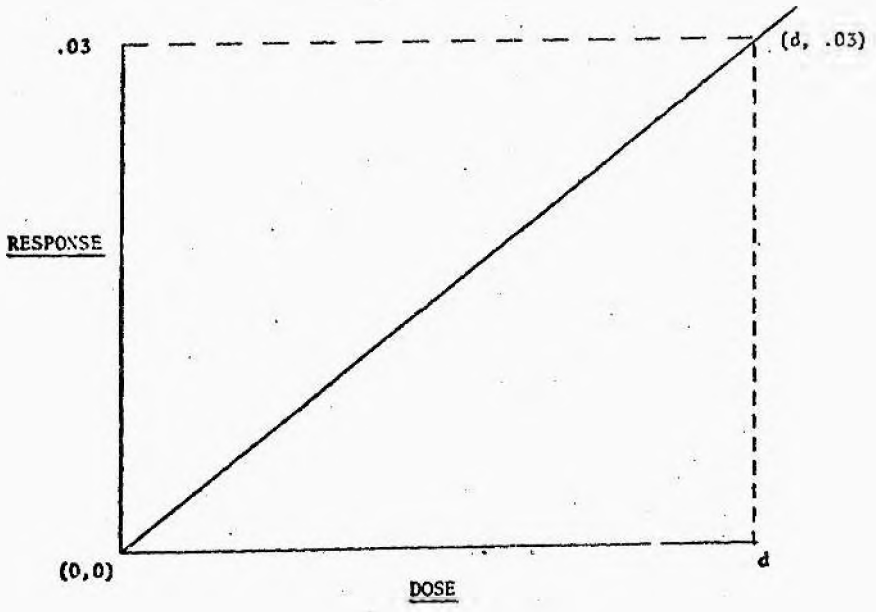
In establishing the concept of an "acceptable" risk dose (ARD) we must bear in mind that the dose level arrived at gives a tolerable risk *only for the species for which the extrapolation has been made.* Given this caveat, to make a conservative[4] estimate of an ARD, two assumptions need to be made:

A. The dose-responsive curve at low response levels is concave upward (e.g. the left-hand tail of the common S-shaped curve). The upper (dose) limit of this S-shaped curve is a straight line going through the 0,0 point (no dose= no response). The true dose-response curve is shallowest at this point.

B. A given set of data will provide an estimate for the upper limit of the other point through which the straight line must pass (which then gives the upper limit of the slope of the dose-response curve).

As an example of the use of the ARD concept, let us suppose that we have observed 100 control animals and 100 treated animals at a given dose rate, d, and have seen no tumors in either group. The upper 95% confidence limit on such a result is 3/100 (i.e. the data are consistent with the statement that with a true response rate of .03, we might expect to see zero tumor incidence in 95% of similar experiments). If the socially "acceptable" risk selected is to be one additional cancer case for each hundred thousand persons, it is now desired to establish an ARD which will produce a maximum lifetime tumor incidence of 1/100,000. We can then construct the graph:

[4] The procedure outlined here is essentially the "one-hit" procedure and gives a somewhat more conservative answer than the procedure of Mantel and Bryan (4).



The line connecting the (0,0) point with the (d, .05) point has

$$\text{Slope} = .05/d$$

and the equation of the line is:

$$\text{Response} = (\text{Dose})\,(.05/d)$$

If we wish to determine some dose (e.g. the ARD) which would be predicted to yield a response of not more than $1 \cdot 10^{-5}$ we would write:

$$\text{Dose} = (1 \cdot 10^{-5})\,(d/.05) = 3.3 \cdot 10^{-4} d$$

ARD

Working towards an ARD this way has several consequences:

a. An increase in the experimental size (at the same dose, d, and with the same experimental result, i.e. no tumors) will reduce the upper confidence limit. Thus, if there were 200 animals in each contrast group, the upper 95% confidence limit would be about halved and the estimated ARD would be doubled.

b. An increase in the dose, d, at which the result (no tumors) occurred would increase the estimated ARD in direct proportion to the tested dose. Thus, if the initial experiment had been conducted at twice as high a dose *with the same result*, the estimated ARD would be twice as high as that determined from this experiment.

The procedure outlined has the virtue of lending greater credence to conclusions reached on the basis of larger experiments. Higher estimated ARD's will be found under such circumstances and the confusion between "not statistically significantly different", and "not different" can be avoided.

It must be stressed that these calculations do not establish an "acceptable risk dose" for man. The procedures do not tell us for example what factors are required to extrapolate from animal to man, although the following factors must certainly be considered.

1. Dose-response curves in man (a grossly non-homogeneous animal) are likely to be much shallower than dose-response curves in experimental animals. This implies higher levels of response at low doses for man, other things being equal.

2. It is possible that even the use of the straight line between the 0,0 point and some experimentally determined dose-response point (plus upper confidence limit) may yield too high an estimated ARD for man.

3. Whether the proper blow-up factor for doses in man should be on a mg/kg or mg/M^2 basis, or any other basis, must be established independently.

4. Nothing in this procedure would enable one to know where the dose-response curve for man belongs along the dose scale in comparison with the dose-response curve for the experimental animal. If man's curve lies much to the left of the experimental animal's curve, then an ARD for the experimental animal may be a gross overdose for man.

Where several species are studied, it would seem safest in the absence of better information, to accept for man an ARD no greater than the lowest ARD dose derived from the results for the several species. It has been suggested that an appropriate "safety factor" for man should involve a reduction in the ARD for animals by a factor of 100 to allow for species' differences, another factor of 100 to allow for interactions with other carcinogens, and another factor of 100 to hedge against the incorrect choice of "blow up" (weight, or surface area) from animals to man. This would imply an ARD in man of about 1×10^{-6} the ARD in animals.

INSTRUCTIONS FOR CALCULATION OF THE ARD USING 95% AND CONFIDENCE LIMITS

(Experiment in which no animals in either treated or control group show a response, e.g. development of a tumor): We need the following values:

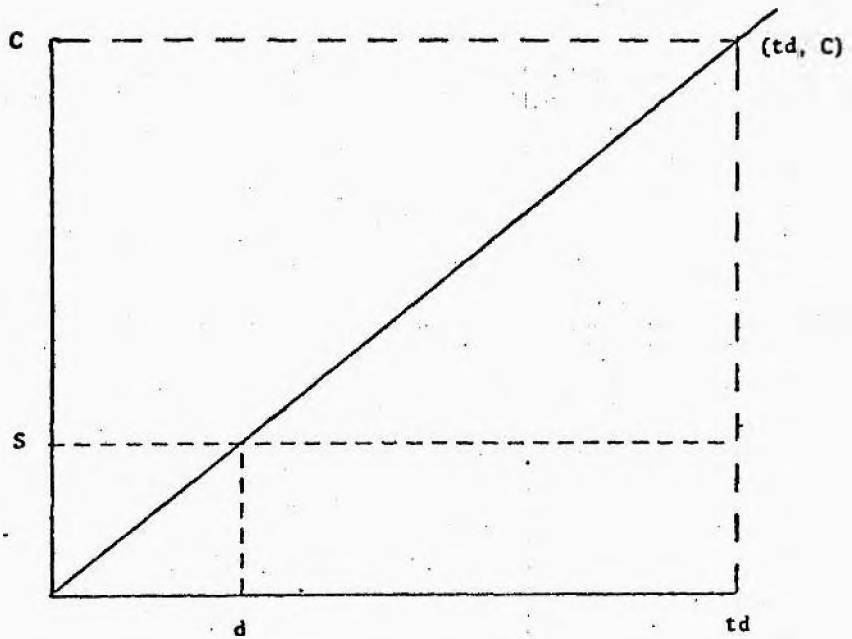
C=Upper confidence limit on the result (computed as shown below).

S=Arbitrary "acceptable" response level.

d=Acceptable risk dose (ARD), that which causes no more than the arbitrarily allowed acceptable risk.

t d=Test dose, some multiple, t, of the tolerated dose.

These values are related as shown:



From the above figure, we have the following relationships: $C/S=(t\cdot d)/d=t$ which can also be stated as $C=St$.

Since C is a function of the size of the experiment, N, we have a relationship between S, t, and N where N=sample size.

For zero positive responses, the upper a% confidence limit is $St=C=1-e[\ln(1-a)]/N$, where ln is the natural logarithm. From this relationship, given any two of the values N, t, and S, we can solve for the third. The accompanying graphs have this relationship shown for difference values of N. Figure A1 s for a 95% confidence limit: Figure A2 is for a 99% confidence limit.

In any specific situation St is constant (=C), so that we can increase the range of the chart by dividing S (the tolerable risk level) by k while multiplying t (the dose multiplier) by k. Two sets of values for S and t are shown on each graph.

EXAMPLES OF HOW TO USE GRAPHS

1. Given:

a. That we agree to a socially "acceptable" risk level, say .00001 (1 in 100,000).

b. The expected average dose in man is D, and we wish to determine whether it is compatible with the acceptable risk.

c. The maximum pharmacologically tolerated dose in our test species is tD, where, say, t=600, (i.e. this species can survive a dose 600 times larger than the average dose in man).

Procedure (Using "95%" figure)

a. Find t=600 along the bottom scale of the graph. Notice that it is in parenthesis. This means we must look for our S value in parenthesis, too. (Small arrow at bottom of graph.)

b. Find $S=10(\times 10^{3})$. (Small arrow at side of graph.)

c. Find where the t=600 vertical line crosses the S=.00001 horizontal line. This is at the diagonal line labeled 500.

This means we must conduct an experiment with 500 animals in each group, yielding 0 positives, at a dose level 600 times the "average" dose in man, in order to have some assurance that the average dose in man is within the acceptable risk level, where acceptable risk is .00001. [This dose may be far too high, for it has been assumed that man's dose-response curve is the same (except for slope) as

the animal species in which we did the experiment. No "safety" factors have been applied.]

2. Given

To repeat the above experiment using a dose 300 X the expected ARD. S=.00001, and t=300.

Procedure

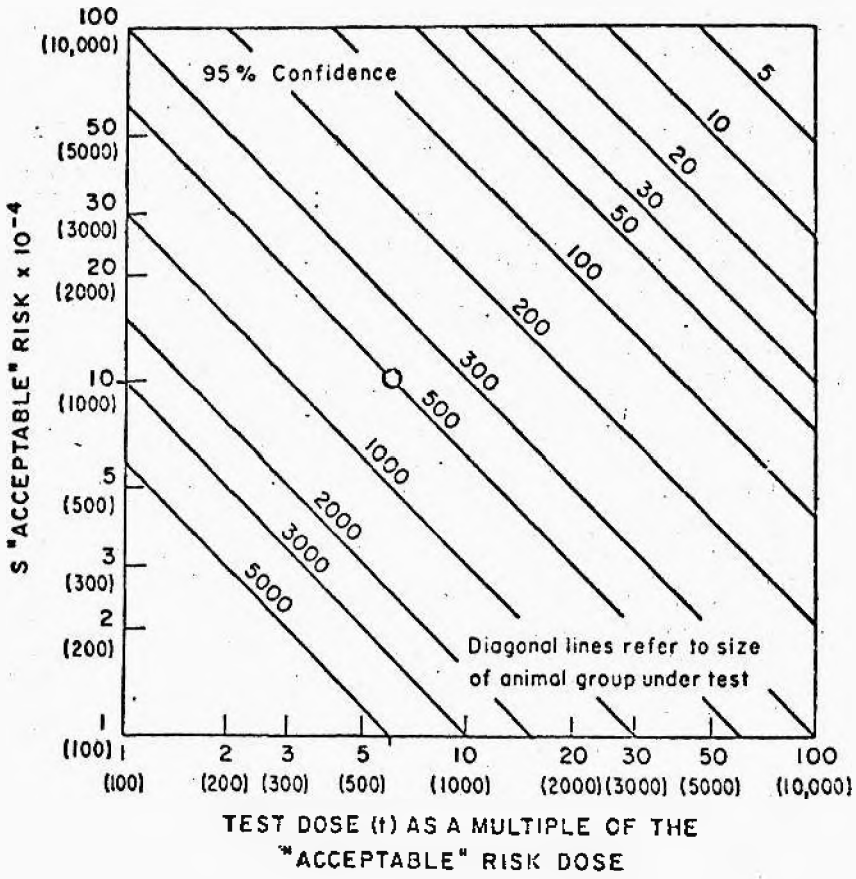
Find t=300 along the bottom scale (in parenthesis).
Find S=10($X 10^{-4}$)
Note the crossing point at diagonal N=1000.
This means if we test at a lower dose, we must have more test animals to achieve the same ARD.

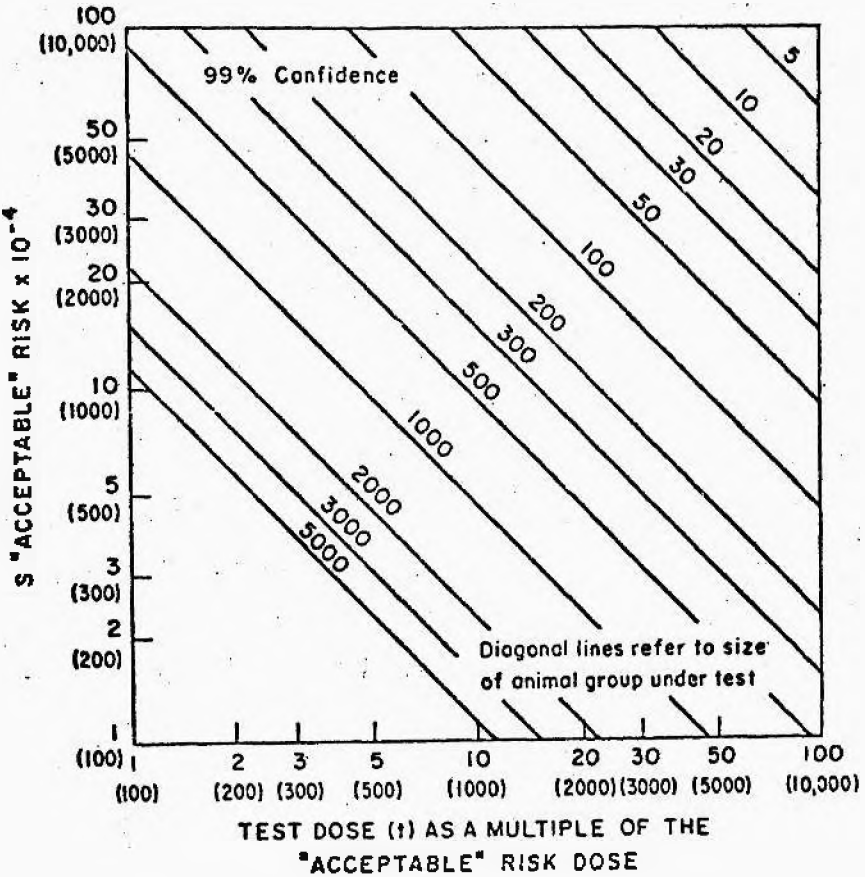
3. Given

To repeat experiment *1* using only 100 animals. N=100; S=10($\times 10^{-4}$)

Procedure

Follow along the horizontal line until you come to diagonal N=100
Look down to the t scale and note that we are at t=3000.
This means if we test with fewer animals, we can have assurance only that a dose 1/t times the test dose will yield less than the acceptable level. Fewer animals in a test imply a lower ARD. In this case the ARD is 1/3000 the test does as compared with 1/600 in Example 1.





Appendix IV—Relationship Between Chemical Analysis, Biological Assays and Carcinogenic Risks to Man

The following set of Figures presents a conceptual scheme for dealing with the problems stated. In practice any or all of the steps may be rendered impossible by limitations in quantifying pertinent variables. Operational problems in implementing the plan result from uncertainties in the correspondence of human and animal dose response curves, extrapolation of animal data to extremely low response levels, differences in response from species to species, synergistic effects, etc. The scheme itself may be useful, however, in defining the specific areas in which further efforts should be made.

Problem No. 1: Given the Presence of a Chemical in the Environment, Estimate Its Carcinogenic Hazard for Man and Determine Its Compatibility With a Socially "Acceptable" Risk

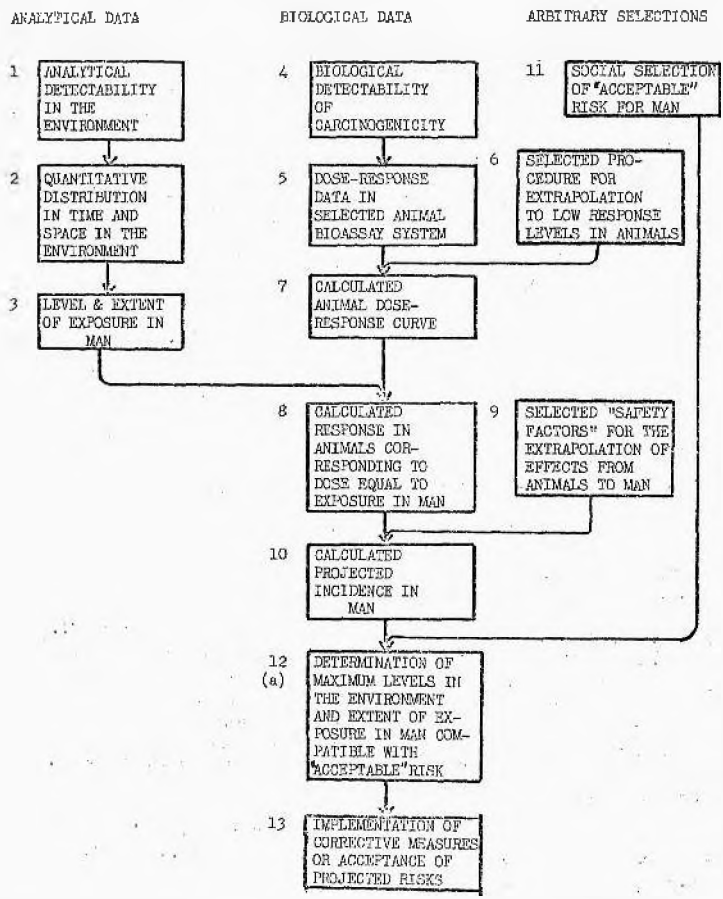
The inputs and the estimations required for this problem are represented in Figure 1 and discussed in the following paragraphs.

1. Analytical Detectability in the Environment—Limited by the sensitivity and specificity of the available analytical method.

2. Quantitative Distribution in Time and Space in the Environment—Preparation of "environmental profiles" limited chiefly by extent of sampling. Segments of the environment should not be considered non-contributory, because they fall below the minimum levels for analytical detection.

PROBLEM NO. 1 - GIVEN THE PRESENCE OF A CHEMICAL IN THE ENVIRONMENT, ESTIMATE ITS CARCINOGENIC HAZARD FOR MAN AND DETERMINE ITS COMPATIBILITY WITH A SOCIALLY "ACCEPTABLE" RISK.

INPUTS:



BOX NUMBERS REFER TO TEXT

FIGURE 1

8. Calculated Response in Animals Corresponding to a Dose Equal to Exposure in Man—Obtained by calculation from Items 3 and 7. This provides the basis for the extrapolation from the response in animals to that in man in Steps 9 and 10.

9. Selected "Safety Factors" for the Extrapolation of Effects from Animals to Man—This selection is of necessity an arbitrary one, but it must be based on informed judgment. It is severely limited by our lack of specific information on effects in man, and should be made so as to avoid underestimating the risk. The choice of a safety factor of 100, frequently applied in cases of reversible toxicity, is inadequate to cover the complex assessment of carcinogenic risks in man. A factor should be applied for at least each of the following parameters: species susceptibility, interaction and potentiation effects, correction for animal size or body weight.

10. Calculated Projected Incidence in Man—Obtained by calculation from Items 3, 8, and 9, i.e., by taking the level of exposure in man, calculating the tumor incidence that this level of exposure would produce in the animal, and multiplying it by the total selected "safety factor".

11. Social Selection of "Acceptable" Risk for Man—This arbitrary selection is a determining element in the process of decision. It must be based on the most extensive information available on the consequences of accepting a given risk and on the projected "benefits" that would result.

12. (a) Determination of the Maximum Levels in the Environment and Extent of Exposure in Man Compatible with Socially "Acceptable" Risks—Compare Items 10 and 11; if projected incidence in man is greater than acceptable risk, determine what level of exposure in man (Item 3) would give an incidence in man (Item 10) equal to or lower than the acceptable risk (Item 11). Exposure can be reduced by changes in the environmental levels and distribution, or by reducing the number of people exposed.

13. Implementation of Corrective Measures, or Acceptance of Projected Risks—Implementation of corrective measures necessary to reduce the projected risk to a socially acceptable level may be extremely difficult. In such cases, the extent of the risk should be clearly stated and a continuing effort developed towards control of the problem.

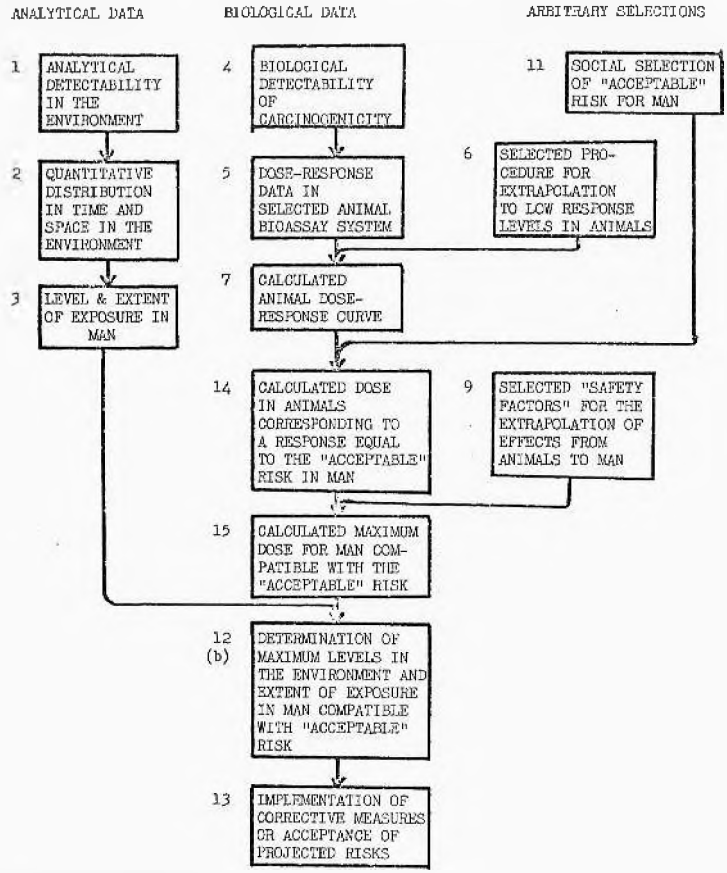
PROBLEM NO. 2: GIVEN A PROPOSAL TO INTRODUCE A CHEMICAL INTO THE ENVIRONMENT, ESTIMATE THE MAXIMUM EXPOSURE LEVEL FOR MAN COMPATIBLE WITH A SOCIALLY "ACCEPTABLE" RISK

The inputs and estimates required for this problem are represented in Figure 2. The same definitions used for Problem 1 apply. Two different calculations are involved, those in steps 14, 16, and 12(b).

14. Calculated Dose in Animals Corresponding to a Response Equal to the "Acceptable" Risk for Man—Obtained by calculation from items 7 and 11.

PROBLEM NO. 2 - GIVEN A PROPOSAL TO INTRODUCE A CHEMICAL INTO THE ENVIRONMENT, ESTIMATE THE MAXIMUM EXPOSURE LEVEL FOR MAN COMPATIBLE WITH A SOCIALLY "ACCEPTABLE" RISK

INPUTS:



BOX NUMBERS REFER TO TEXT

FIGURE II

1. Factual information on the sensitivity of analytical methods and on the extent of environmental distribution and of exposure in man (Items 1, 2, and 3).

2. Factual information on the limits of the biological determination of carcinogenicity, represented by the sensitivity of bioassay methods, the significance levels of the results obtained, and the dose-response data (Item 4, 5).

3. Documentation of the criteria and procedures used for the selection of the arbitrary factors used in the evaluation process. These factors include the selection of a socially "acceptable" risk, of a procedure for dose-response extrapolations in the animal model and of "safety factors" for the extrapolation from animal to man (Items 6, 9, 11).

Only in the case of substances for which we have extensive analytical environmental data and extensive bioassay results (probably including a dose-response study of acceptable quality) can we attempt the exercise of estimating some dose corresponding to an "acceptable" risk for man. This can only be done by clearly stating the justification for each of the arbitrary extrapolation factors chosen. The selections will be justified only if they represent an upper limit of risk acceptance, that is, if they assure us that the risk in man is not underestimated.

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