Human Health Hazards Associated with Chemical Contamination of Aquatic Environment

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Given the finite supply of water available for human use, continued chemical contamination of the aquatic environment may pose a significant human health hazard. Consequently, an effort must be made to develop ambient water quality criteria to protect human health and preserve the integrity of the aquatic environment. In developing water quality criteria based on human health effects, information on sources of exposure, pharmacokinetics, and adverse effects must be carefully evaluated. Information on sources of exposure is needed to determine the contribution of exposure from water relative to all other sources. Pharmacokinetic data are used in inter- and intraspecies extrapolation and in characterizing the mode of toxic action. Information on toxic effects includes data on acute, subchronic, and chronic toxicity, mutagenicity, teratogenicity, and carcinogenicity. In analyzing such information, a distinction is made between threshold and nonthreshold effects. Currently, carcinogenicity and mutagenicity are considered to be nonthreshold effects. For carcinogens and mutagens, criteria are calculated by postulating an "acceptable" increased level of risk and using extrapolation models to estimate the dose which would result in this increased level of risk. For other chemicals, thresholds are assumed and criteria are calculated by deriving "acceptable daily intakes" for man which would presumably result in no observable adverse effects. Neither process is exact, and attempts must be made to improve and verify risk assessment methodologies.

Introduction

The importance of assessing health hazards associated with chemical contamination of the aquatic environment continually increases. There is an urgent need to maintain water quality. The earth is a closed system with finite resources (1). The total amount of water on earth is estimated to be about 1500 million cubic kilometers, but 97.134% represents ocean waters while the remaining water is captured as icecaps (2.225%), as glaciers (0.015%), and groundwater (0.6%). Freshwater lakes contain 0.009%, while rivers contain only 0.0001% of the earth's total usable fresh water (2, 3). These sources, along with a small amount of underground water, represent all of the water that is available for human use today.

The level of technological development in individual countries is the paramount reason for variations of water quality and its overall utilization. The United States is a good example of excessive water usage due to advanced technological development. At the beginning of the century, water usage in the U.S. was estimated at 500 gal/person daily (4). If we could consider an identical population in 1970, this amount has increased more than three fold, to 1800 gal. However, due to the increase in the U.S. population, an eightfold overall increase of 50 to 400 billion gallons of water used daily has occurred over that time period (4, 5).

Based on an estimate by Doxiadis in "Water for Peace" concerning yearly worldwide demand for water per capita, the U.S. population will use three times as much water as the rest of the world population by the year 2000 (5, 6). Even more dramatic increases in the use of water could be expected on a global scale during the next decade. Rapid technological development of the underdeveloped nations due to additional hygienic and industrial re-
requirements will be the largest factor in increasing the demand for water. As a result, in the year 2000 the total water demand each year is estimated to be approximately 6500 cubic kilometers, still far below the available amount of water on earth (3, 6). Yet, because of the increasing pollution of waterways by chemical compounds from industrial and municipal sources, we must manage our water resources carefully. The price of technological progress is underlined by recently published data which demonstrated that in the U.S., 72% of all water basins are contaminated by industrial pollutants (7). The Northeast and the Great Lakes regions are affected most; 88% of the water basins are polluted, as compared with 65% in the other areas of the nation (Table 1). In the Southwest 23% of the water basins were shown to be polluted by industrial discharges. In many instances, the specificity of pollution is directly related to geographic location. For example, in the Northeast, Great Lakes, and North Central regions, where heavy industries are located, effluents containing high concentrations of toxic metals and specific organic chemicals are more common. The monitoring surveys in these areas identified heavy metals in 55% of the water basins and other toxic pollutants in 40%. These values compare with 23% and 15%, respectively, for the rest of the country.

Scientific investigations identifying effects of organic chemicals in drinking water have only increased significantly during the past few years, even though carcinogenic substances in industrial waste discharged into rivers and lakes were reported more than 20 years ago by Middleton and Rosen (9), Hueper and Conway (10), and others (11). More recently, a number of carcinogenic substances were identified in chlorinated municipal sewage effluents (12). Pollutants from industrial effluents and municipal sewage contaminated water supplies on a continuous basis. Dumping and accidental spills have polluted waters on an intermittent basis, also contributing significantly to the pollution levels of water basins (13). Furthermore, various monitoring studies have identified the presence of carcinogens in treated municipal drinking water (14-18). Preliminary epidemiological data from Louisiana, Ohio, and New Jersey indicate that water polluted by organic chemicals from industrial, municipal, and agricultural sources contains a large number of potential carcinogens. Although the measured levels have been rather low, they have been shown to be increasing over the past 25 years. Unless appropriate control technologies are used, it is entirely possible that the increasing level and number of hazardous chemicals in water will result in significantly increased health risks to the population (19, 20). Evidence of the constantly increasing numbers of chemicals in water and the resulting potential hazard to public health, has been clearly documented.

As a part of the Toxic Substances Control Act, the EPA has been charged with maintaining an inventory of chemical substances manufactured, imported or processed in the U.S. for commercial purpose (21). The EPA has contracted with American Chemical Society Abstracts Service (CAS) to process all the reports and to create and maintain a file on all chemicals and their manufacturers. To date, according to CAS, scientists have identified more than 4.3 million chemicals. The report stated that the number of chemicals in the world register has been growing at an average rate of about 6000 per week. Furthermore, it was estimated that, not including pesticides, pharmaceuticals, and food additives, more than 50,000 chemicals are marketed and are in everyday use (21). Approximately 63,000 chemicals are used commercially today. Of the newly registered chemicals, approximately 1000 new compounds enter the

| Region       | Number of basins | Percentage affected by type of source |
|--------------|------------------|---------------------------------------|
|              |                  | Industrial | Municipal | Combined sewer overflow |
| Northeast    | 40               | 95         | 95        | 60                      |
| Southeast    | 47               | 74         | 91        | 17                      |
| Great Lakes  | 41               | 80         | 95        | 37                      |
| North Central| 35               | 74         | 86        | 6                       |
| South Central| 30               | 70         | 100       | 0                       |
| Southwest    | 22               | 23         | 64        | 0                       |
| Northwest    | 22               | 55         | 73        | 14                      |
| Islands      | 9                | 89         | 100       | 0                       |
| Total        | 246              | 72         | 89        | 20                      |

*Data of U.S. Environmental Protection Agency (8).

*In whole or in part.
marketplace worldwide each year; 300-700 of these in the United States alone.

Improved analytical techniques have allowed the detection of reported carcinogenic contaminants at lower (microgram) levels. Kraybill (22) has published a comprehensive review on the global distribution of carcinogenic pollutants in water. From his report it is clear that the use of modern techniques such as gas-liquid chromatography and mass spectroscopy has improved significantly the identification process of organic chemicals in water. As a consequence, we are constantly accumulating evidence that man is chronically exposed through ingestion of water to many more chemical agents than we were able to identify originally. Even though the exposures are at extremely low levels, it is possible that an increase of detrimental biological effects may be reported in the future. Further conclusive toxicologic and epidemiologic evidence is needed before many suspected compounds can be proven hazardous to man at the levels presently encountered. These data are urgently needed for the appropriate regulatory actions.

Although this paper will focus on the development of ambient water criteria to protect human health, the principles used are similar to those encountered in evaluating potential effects on aquatic life. Both human and aquatic health assessments involve extrapolating results of observable responses in test species to projected or acceptable levels in the species of concern (target species). Although the principles of extrapolation are similar in both types of risk analysis, certain practical differences between human and aquatic risk assessment exist and should be appreciated. In terms of the target species, human health hazard assessment attempts to convert a risk from various mammalian species to only a single species, *Homo sapiens*. Aquatic hazard assessment is concerned with the effect of xenobiotic stress in aquatic communities, groups of species interacting by mechanisms which are neither readily quantified nor clearly understood. In this respect, ecological hazard assessment is more complex than human hazard assessment. However, since society is understandably most concerned with human health, the level of acceptable risk is usually much lower in human risk assessment than in aquatic risk assessment. Consequently, the degree of high-to-low dose extrapolation is usually much greater in studies designed to detect human risk. Perhaps most importantly, human hazard assessment is usually based on studies using animal species that are not closely related to humans, such as rats or mice. In aquatic risk assessment, data are sometimes available on test species which are closely related or identical to target species. Given the multiplicity of species involved in ecological hazard assessment, the uncertainties of high-to-low dose and experimental mammal-to-man extrapolation involved in human hazard assessment, it is often extremely difficult to develop a sound hazard analysis (23). Consequently, it is incumbent on both mammalian and aquatic toxicologists to work closely together to clarify and improve risk assessment methodologies within their own disciplines.

**Scientific Basis for Risk Assessment in Man**

The objective of health effect assessments, which form a basis for water quality criteria, is to estimate ambient water concentrations which would protect the public health. Ideally, the criteria should represent levels for chemical compounds in ambient water which would not pose any hazard to the human population. However, in any realistic assessment of human health hazards due to environmental chemicals, a fundamental distinction must be made between absolute safety and acceptable risk. Criteria for absolute safety would have to be based on detailed knowledge of dose/response relationships in humans including: all sources of chemical exposure from the various environmental media, the types of toxic effects elicited due to specific pollutants or their mixtures, the existence or nonexistence of "thresholds" for specified toxic effects, the significance of interactions (synergistic or antagonistic), and the variances of sensitivities and exposure levels within the human population.

Rall (24) and many others have used the famous quote by Alexander Pope: "The proper study of mankind is man." Obviously, the best data for estimating human risk are obtainable only from man. However, humans cannot be used directly as experimental subjects for toxicologic evaluation of carcinogens and other hazardous substances for obvious sociological, medical-ethical and legal reasons. Therefore, lower mammals and other biological systems must be used. The results are then extrapolated to evaluate as closely as possible the risk in human populations. Consequently, those involved in risk assessment programs must extrapolate interspecies, from the rather limited knowledge of effects in animal systems to unknown effects in another species (human). They must deal, at the same time, with many additional difficult intraspecies factors that occur. Available results usually demand extrapolation from limited data on small groups of animals exposed to high dose levels for short periods of time to human populations exposed to low levels of environmental agents over prolonged periods (25). Even the extrapolation process from
human clinical studies, which bypasses the interspecies extrapolation problems, presents many difficulties because the data points are usually available for only a few human subjects, who are often ill and under medical treatment for a different reason. It is difficult to project such data to the U.S. population of over 200 million people. On the other hand, epidemiologic studies of larger populations almost always lack dose-effect relationship data. In practice, definitive criteria derived directly from human subjects can seldom be established because of deficiencies in available information and in the technical means of data interpretation. As a consequence, extrapolation methods from animal data and various statistical methods need to be used to derive health effect criteria which may estimate the minimal or specified risk of chemical substances in ambient water to man.

In order to develop a comprehensive approach to health hazard evaluation of chemical contaminants in ambient water, it is necessary to collect and classify all available and pertinent information on the subject (26). Sufficient conclusive data are, however, seldom available for most contaminants of water. In a majority of cases there is a paucity of relevant data, and scientific judgment as well as policy decisions must play a role in establishing acceptable levels of population exposure. The minimal data base for this purpose should include information on: sources of exposure which reviews available monitoring data of present levels of hazardous agents in the aquatic environment; pharmacokinetic data on the agent, including all available metabolic data in humans and experimental animals; and dose-related adverse effects reported in man and other biological systems.

Sources of Exposure

The exposure section should contain all available monitoring information of the current levels of human exposure to the individual pollutant from all sources, including ambient water. The major purpose of this section is to provide background information on the contribution of exposure from water, relative to all other sources. Consequently, this section is subdivided into exposure from ingestion in water, ingestion in food, inhalation, and dermal contact.

Evaluation of the present population exposure is an extremely valuable part of the approach for the development of water quality criteria. Man can be exposed from daily consumption of water as well as from ingestion of contaminated aquatic organisms, each factor contributing to the total exposure. For this purpose, certain assumptions must be made.

The most appropriate approach is the use of reviews and recommendations of scientific committees and organizations, such as the NAS monograph on drinking water and health (26). The U.S. Environmental Protection Agency, for example, has recently, under a court order, formulated criteria for 65 chemicals identified as water pollutants (27). Useful assumptions taken from the NAS publication concern human daily exposure for criteria calculations. Average ingestion of 2 l/day of water over a lifespan of 70 years was used as proposed by the NAS committee (26). The average consumption of specified fish and shellfish products was estimated to equal 18.7 g/day (28). The consumption of fish products is an important exposure factor; it requires a satisfactory estimate of the amount of pollutant residue in the edible portion of the ingested aquatic organism. Bioconcentration factors are used to quantify the pollutant residue in aquatic products of the chemical in ambient water in which the organism lives. This factor has a direct influence on the determination of the final criteria level, especially if the bioconcentration factor is large.

In general, knowledge of exposure from all sources is needed in recognizing the contributions to total body intake from all exposure routes. Additional information relative to special population groups at risk, based on unusual individual susceptibility or unusually high levels of exposure in specific segments of the population must also be given consideration. Most importantly, the relationship between present levels of exposure to ambient water contaminants and the calculated criteria must be carefully evaluated to determine if a human health hazard exists.

Pharmacokinetics

Data on the pharmacokinetics of environmental pollutants in humans and experimental mammals are extremely useful in inter- and intraspecies extrapolation, especially in assessing the magnitude of body burden from long-term low-level exposures, and in characterizing the mode of toxic action (29). Information on absorption and excretion in animals, together with a knowledge of ambient concentrations in food and water, may be used to determine body burdens of chemicals in man. Distribution data are of great importance in determining target organs or tissues. They may provide supportive evidence for the validity of species-to-species extrapolation. For instance, if an agent has been shown to have similar distribution in both experimental animals and humans, the toxicity data can be extrapolated to humans with much greater confidence (25). Determination of the metabolic pathway and eventual fate
of the test chemical is important in assessing a potential additional health impact of chemical compounds since metabolites may exert a greater toxic effect than the original agent (30). Finally, the knowledge of the rate of excretion and the resulting biological half-life may also have a bearing on the biological effects of the agent.

Effects

Toxicological evaluation of environmental pollutants is based on qualification and quantification of the observed health effects in humans and experimental animals. In an attempt to organize the magnitude of various toxic manifestations, the scientific community (29, 31) has established the following classifications of effects: (1) acute, subchronic and chronic toxicity; (2) mutagenicity; (3) teratogenicity; (4) carcinogenicity. Technically, all four groups of effects are “toxic.” The main difference between acute, subchronic, and chronic toxicity and the other three categories is that the latter three, namely, mutagenic, teratogenic and carcinogenic effects may involve the genetic system.

In terms of the magnitude of hazard, all adverse effects may be divided into transient/reversible or persistent/irreversible. The National Academy of Sciences Safe Drinking Water Committee (26) defines a “reversible” effect as one which disappears after exposure ends, i.e., within a timespan that comprises only a small fraction of the organism’s lifetime. The concept of reversibility implies that there is a no-effect level or that there exists a dose below which human health will not be compromised. “Irreversible” effects can be divided into two categories based on severity. In the first group, the adverse response either does not regress completely or progresses after exposure ceases. The second group of irreversible harmful changes can be defined as those that are likely to be life threatening even after exposure has ceased. It includes terata, malignant tumors, mutations in offspring of exposed animals, and some neurological changes. Although irreversible effects usually pose the greatest risk to human health, a frequently recurring reversible effect may result in as high or higher mortality than irreversible effects which appear later in life.

Toxic Effects

Toxic effects are classified as acute, subchronic, or chronic, based on duration and level of exposure. The quantitation of the lethality of substances is an established approach in classical toxicology and represents the first critical step in the health assessment and safety evaluation of chemicals. Acute toxicity data provide the initial ranking of chemicals as to their potential toxicity and serve as a basis to establish critical dosage range for the subchronic and chronic tests at lower doses, including the “no observable adverse effect levels” (NOAEL) (25). Additionally, the acute tests may provide initial gross physiological and pathological evidence of toxicity for structurally similar chemical compounds and identify the target organs or tissues of the compounds (29). Even though acute lethal effects have limited usefulness in hazard assessment, in many instances only acute data are available on a number of chemical contaminants. Regulatory agencies must evaluate and classify all toxicity data in an attempt to develop risk estimate and pollution control strategies. A constantly increasing number of scientific panels and committees have outlined specific procedures for acute testing (26, 29, 32). Attempts have been made by scientists (33, 34) to project from short-term acute test data the potential of a substance to produce chronic low level effects.

Subchronic toxicity testing is performed to establish the nature of the toxic effects, including metabolic behavior of the substance, its bioconcentration, and its retention time in the body. Subchronic testing should provide data to estimate the maximum “no-effect” level and the minimum toxic dose (MTD), as well as pharmacokinetic parameters (25, 29). They are more relevant for characterization of the physiological and pathological lesions caused by the agent under test. The duration of subacute studies varies from days to months. The general approach recommended for these intermediate tests is a period of about 10% of the test animal’s lifespan, i.e., 90 days for a rat living 30 months, 7 years for a human with a 70-year life expectancy (35). The dosing pattern for subchronic toxicity testing should include a dose which will not produce demonstrable effects, and at another end of the range one which is expected to produce a frank toxic, but not lethal, response as well as several (usually two or three) intermediate doses. The “frank effect” dose has often been found to fall between 10 and 25% of the LD\textsubscript{50}, depending usually on the slope of the acute dose response curve (29, 34). The results of subchronic tests are used to determine the desirability of conducting chronic studies and they provide a necessary background for the proper design of these studies.

Chronic Studies. The decision to initiate a long-term low-level toxicity study in experimental animals must be based on several factors (25, 29, 31). The selection of an agent must include a detailed evaluation of environmental persistence, level of contamination, and ubiquity of the substance to be tested; and further, a selection cannot be satisfacto-
rilily made without adequate acute and subchronic data. If available, two approaches are used to evaluate the human effects of long-term low-level exposure to environmental pollutants: (1) epidemiological studies in humans, and (2) long-term experiments on animals exposed to well-defined low levels of the agent (26). Currently, chronic exposure in animals is generally considered to require at least half the animal’s lifespan. However, because of the vast differences in lifespan between humans and experimental animals, chronic tests should be conducted over the animal’s entire lifespan which will maximize the possibility for appearance and observation of adverse effects.

**Teratogenicity.** Teratologic research has been given great emphasis only after Lenz (36) and McBride (37) reported the appearance of severe malformations in newborn infants following administration to the pregnant mother of a presumably harmless sedative, the hypnotic drug, Thalidomide (38). Although teratogenic and other reproductive effects are receiving increasing attention by scientists and regulators, teratogenic effects in man attributable to environmental contamination have not been thus far documented.

One of the problems with teratogenicity studies is the failure to clearly distinguish fetal teratogenicity from embryonic lethality and fetal toxicity (39). A teratogen is defined as a compound that “causes structural or functional birth defects.” Fetal toxicity is essentially measured by the reduction in fetal growth. Embryolethality is represented by the number of resorptions and abortions representing fetal deaths. One of the most important factors in teratogenicity studies is the observation of the relationship between maternal toxicity and fetal toxicity (40).

Even when these distinctions are maintained, difficulties with experimental design remain. As with most biological studies, adequate numbers of animals must be used to permit valid analysis (41). In this regard, primates are often prohibitively expensive and not easily available in sufficient numbers. Consequently, most teratogenic studies utilize rodents. Such studies usually must involve at least 20 pregnant females per dose level and always use the litter as the experimental unit. The chick embryo is not highly regarded as a good model for the estimation of teratogenic risk of chemicals to humans because the yolk sac is a closed system which accumulates chemical substances with a long residence time. As test systems improve to predict potential human teratogens, this biological endpoint is likely to prove of greater significance in estimating human health hazard (39).

**Mutagenicity.** The use of screening methods (in

vitro/in vivo combination systems) in qualitative toxicological testing has increased in importance in recent years. Various approaches have been recommended in the literature to use available screening techniques singly or in a battery of tests for preliminary evaluation of chemicals for their mutagenic and carcinogenic potential before expensive long-term bioassays are initiated (29, 31, 42). The Food and Safety Council (29) in their recent report listed three objectives in mutagenic assays of chemical compounds: (a) does the chemical have the capability to induce heritable genetic effects in man, (b) can the risk of the agent on mutagenic potential in man be quantitated and (c) can the data derived from mutagenicity tests be used for the prediction of toxic effects in vivo, specifically, the induction of cancer. They suggest a test battery in vitro and in vivo such as (1) assays for induction of point mutations using microbial and mammalian cell tests, incorporating in vitro activating system; (2) tests for induction of chromosomal changes; (3) assays for induction of unscheduled DNA synthesis and/or DNA repair in mammalian cells; (4) tests for induction of point mutations by host mediated assay using microbial or mammalian cell systems as indicators; (5) testing of body fluids using microbial indicator systems; (6) tests for in vivo induction of chromosomal changes by direct cytogentic analysis of metaphase; (7) micronucleous tests; (8) dominant lethal tests; (9) assay for cell transformation using in vitro cultured mammalian cell lines. The committee has also outlined criteria for judging a substance to be a mutagen. They suggest that if any in vivo tests in the intact animal or any two of the in vitro tests are positive, then a substance must be considered a mutagen and further, that such results indicate a need for long-term in vivo testing for carcinogenicity (29).

Presently, for a satisfactory evaluation of the carcinogenic hazard of chemical compounds, the testing cannot be based on short-term mutagenicity nor on in vitro carcinogenicity data, but only on an appropriate bioassay in experimental animals. The interpretation of short-term mutagenicity assay data is a complex matter, and thus far the decision whether a chemical presents a mutagenic risk to man based on these test results is not possible (26).

**Carcinogenicity.** For both societal and scientific reasons, carcinogenicity is at the present time the biological endpoint of greatest concern in environmental hazard assessments. The emotional/psychological primacy of cancer has obvious roots. Cancer is the second major cause of death and suffering in this country. Few families are left untouched by this wasting, irreversible disease. Although there may be many other causes of cancer, such as viruses or unavoidable exposure to natural
compounds or physical agents, epidemiologic studies have clearly demonstrated the ability of chemicals to induce cancers in humans. Scientifically, the concern for cancer focuses on the concept of "threshold." Several reputable scientific bodies have concluded that there is no scientific basis for assuming a threshold or no-effect level for genotoxic chemical carcinogens (26, 29, 43, 44). This stems from the hypothesis that each molecule of a carcinogen can interact with DNA and that this interaction can result in development of a malignant growth. Thus, it is generally accepted that any level of exposure to a genotoxic chemical carcinogen will increase the incidence of cancer in the exposed population. Thus, while all cancers are certainly not attributable to the chemical contamination of the environment, there is ample reason for concern and to control contamination of water supplies by effluent chemicals. 

Although the problem is real, it is difficult to analyze both qualitatively and quantitatively. An approach must be developed to determine if a chemical poses a carcinogenic risk to man and a further attempt must be made to quantify this risk. In order for scientists to exercise their best judgment, three types of data should be used to make a reasonable determination of carcinogenicity: (1) in vitro tests for mutagenicity, (2) human/epidemiological studies, and (3) mammalian bioassays (43, 45). As indicated in the previous section, in vitro tests for mutagenicity can be useful in demonstrating direct genotoxic effects and may serve as useful screening tests for potential carcinogenicity. Direct application of such data to human risk assessment is, however, an inconclusive process given our current understanding of chemical carcinogenicity. Epidemiologic studies can directly indicate that a compound poses a carcinogenic threat to humans; however, the utility of these studies is limited because they most often do not involve satisfactory dose/response information. Therefore, a qualitative determination of carcinogenicity to humans can be made from such studies, but a quantitative estimate of risk is often impossible (25, 26). The use of mammalian bioassays for carcinogenicity represents the most satisfactory approach to human hazard assessment, although difficulties are encountered. On the positive side, mammalian bioassays involve the exposure of organisms similar in some respects to man to defined dose levels under controlled conditions. On the negative side, two major issues must be always resolved: intraspecies extrapolation from high to low dose levels and interspecies extrapolation of data from lower mammals to man. Although these problems are by no means trivial, mammalian bioassay data are the major source of information on potential human risk.

With some exceptions, compounds which are carcinogenic to humans are also carcinogenic to experimental mammals. Since the converse cannot be unequivocally demonstrated, a major effort must be made to verify or develop improved methods for the extrapolation of mammalian data to man.

**Extrapolation and Risk Assessment**

To extrapolate, as defined by Webster (46), is "to project, extend, or expand known data or experience into an area not known or experienced so as to arrive at a usually conjectured knowledge of the unknown area by inferences based on an assumed continuity, correspondence, or other parallelism between it and what is known."

In risk assessment, this process entails postulating a biologic reality based on observable responses and developing a mathematical model to describe this reality. The model may then be used to extrapolate to response levels which cannot be directly observed but which represent acceptable risk. Figure 1, from Gehring (47), illustrates some of the models which have been used in high-to-low dose extrapolation. The solid portion of the curve with its data points represents the observable dose-response relationship. At low levels of response which are directly relevant to human hazard assessment but which are not directly observable in animal bioassays, the shape of the dose response curve is uncertain. As discussed previously, there are reasons to suspect
that genotoxic carcinogens will elicit nontreshold responses so that the dose-response curve will reach zero response only at zero dose (curved dashed line in Fig. 1). Thus, various nontreshold models have been developed to describe the dose-response relationship for carcinogenic chemicals. Some scientists contend that because of repair and detoxification mechanisms (48), certain effects will evidence a real or least practical threshold (49). This type of assumption is illustrated in the two lines which intercept the horizontal axis in Figure 1. The debate over the concept of threshold/nontreshold responses and the different types of mathematical models which can be used to describe these concepts addresses one of the most crucial questions in hazard assessment today (48, 50-53).

In addition to high-to-low dose extrapolation, the extrapolation of data on experimental mammals to potential human hazard is a major difficulty in risk assessment (25, 53). Because epidemiologic studies cannot usually be used to derive criteria and studies in higher mammals are often prohibitively expensive, human risk assessments are usually based on experiments using rodents. Although there are many common features within the mammalian class, differences in xenobiotic metabolism, life span, body weight, gestation period, spontaneous disease rates, as well as a variety of anatomic, physiologic, and biochemical parameters make direct species-to-species extrapolation difficult. For example, in several National Cancer Institute bioassays (45) it was found that some chemicals demonstrate carcinogenic activity in mice but not rats. Further, many strains of mice appear to be particularly susceptible to the development of liver tumors from chemicals which have no apparent carcinogenic activity in other species or organs. Consequently, the importance of liver tumor induction in mice may be questioned and a systematic effort must be made to evaluate the significance of such tumors to human risk assessment.

Criteria Derivation

Because of the uncertainties involved in extrapolation and risk assessment, the regulatory agencies face a serious dilemma. An absolute estimate of chemical hazard cannot be made. Nonetheless, there must be some attempt to reasonably approximate risks posed by chemical contamination of our environment. The alternatives, i.e., no regulation or an absolute ban on chemical contamination, are unacceptable.

In deriving water quality criteria, the EPA has not solved these problems but has attempted to make policy decisions based on a reasonable interpretation of scientific data and principles (27). For carcinogens, mutagens, and in some cases, teratogens, a nontreshold assumption was adopted. Consequently, "safe levels," i.e., levels which will produce no adverse effects, were not established. Instead, water quality criteria for these compounds were based on levels which would presumably cause a specified increase in incremental risk to the exposed population. For all other compounds, a threshold assumption was adopted. In these cases, criteria were derived which would presumably cause no increase in risk and would represent "safe" levels in water. Both procedures involve calculating an "acceptable" daily dose and partitioning this dose between direct exposure from drinking water and indirect exposure through contaminated fish.

The decision to establish a criterion based on a non-threshold assumption was usually made by evaluating information on carcinogenicity and mutagenicity. In general, any chemical which was demonstrated to cause a significant increase in malignant tumors in laboratory mammals was treated as a carcinogen, and a criterion based on a nontreshold assumption was derived. Each carcinogenicity study was carefully evaluated in terms of the experimental mammal tested, the number of animals at each dose level, dose-effect relationships, pathology, route of exposure, duration of exposure, observation period, and adequacy of control groups. All other factors being equal, studies using oral routes of administration (food, water, or gavage) were given preference. The effects of various experimental factors in the derivation of water quality criteria based on the nontreshold assumption are detailed below. When results obtained from well-designed carcinogenicity bioassay data were equivocal, other data were used in assessing the appropriateness of establishing a criterion based on carcinogenic effects. Such data sometimes included mutagenicity and epidemiology studies and/or any information on carcinogenic potential of structurally related chemicals or metabolites. The weight of evidence permits a qualitative judgement concerning carcinogenic potential of a compound.

The nontreshold assumption was applied by use of human epidemiologic or experimental mammalian data for the "one-hit" model recommended in the EPA's Interim Cancer Procedures and Guidelines for Health Risk and Economic Impact Assessments of Suspect Carcinogens (54). The basic dose response model is

\[ P = 1 - \exp \{ -BD \} \] (1)

where P is the probability of getting an observable case of cancer in a lifetime because of exposure to a daily dose D of the compound, and B is a constant
determined by the data. The quantity \( B \) is the only parameter in the model, and it is interpreted as a quantitative indicator of the carcinogenicity of the compound. At low doses (low enough so that \( P < 0.1 \)), \( P \) is directly proportional to the dose \( D \) and \( B \) is the slope of the dose-response line obtained when \( P \) is plotted against \( D \). Because the model approximates a straight line through the origin at low doses, it is sometimes called a linear, nonthreshold dose-response model. It implies that any exposure to a carcinogen, however small, results in some chance of cancer occurrence, and the probability (or the risk) of getting cancer from low exposure increases linearly with the dose.

EPA is aware that other models for risk extrapolation exist and have been used by EPA under other regulatory programs, as well as by other Federal agencies. The “one-hit” model has recently been endorsed by the four agencies in the Interagency Regulatory Liaison Group (43). It is one of the most conservative models available, since it is less likely to underestimate risk at the low doses typical of environmental exposure. Because of the uncertainties associated with high-to-low dose and animal-to-human extrapolation and other unknown factors, and because of the serious public health consequences that could result if risk were underestimated, the EPA believes that it is prudent to use conservative methods to estimate risk in the water quality criteria program.

Several modifications of the basic “one-hit” model are made in developing water quality criteria. The specific equation used to derive water quality criteria is

\[
CR = \frac{\left(\frac{d_L}{L_e}\right)^a \cdot W_{H}(RL)}{- \ln \left[ \frac{1 - P_e}{1 - P_t} \right] \left( \frac{W_H}{W_A} \right)^{1/3} \left[ W_e + (RF) \right]}
\]

(2)

where \( CR \) = water quality criteria (in mg/l), \( d = \) dose (in mg/kg/day), \( L_e = \) length of exposure (in days), \( L_o = \) duration of experiment – surviving animals sacrificed at termination, \( L = \) expected lifespan for test animals, \( W_H = \) human body weight (in kilograms; assume 70 kg), \( RL = \) additional risk over lifetime, \( P_t = \) proportion of test animals with tumors, \( P_e = \) proportion of control animals with tumors, \( W_A = \) average weight of test animals (in kilograms), \( W_C = \) daily water consumption (assume 2 liters), \( R = \) bioconcentration factor for edible portions of fish, \( F = \) average weight of fish consumed per day (in kilograms; assume 0.0187 kg).

This model estimates the concentration of a compound in ambient water which would be associated with a specified increased lifetime risk of a 70 kg human developing cancer from daily drinking 2 liters of contaminated water (26) and consuming 18.7 g of fish taken from contaminated waters (28). Each document in which criteria based on carcinogenic effects are derived presents calculations for a range of risk levels (10^{-7} to 10^{-6}) as well as criteria which include and exclude fish consumption (27).

As indicated in Eq. (2), the estimates of fish consumption and the bioconcentration factor can have a major effect on the criteria. The consumption estimate of fish and other aquatic organisms was based on the recent data compiled by Cordle and co-workers (28) and divided into four categories: freshwater fishes, saltwater fishes, molluscs, and decapods. Three different procedures were used for estimating the bioconcentration factors depending upon the availability of bioconcentration data for the edible portions and the lipid solubility of the chemical (55).

For those compounds which were not reported to induce carcinogenic effects or for those compounds on which carcinogenic effects data were lacking or insufficient, the threshold assumption was applied. In so doing, an attempt is made to define a “no observable adverse effect level” (NOAEL). In many respects, the evaluation of studies used to derive a NOAEL was similar to that of carcinogenicity bioassays. In order to approximate more closely the conditions of human exposure, preference was given to chronic studies involving oral exposures (dietary or in water) over a significant proportion of the organism’s life span. Greatest confidence is placed in those studies which demonstrated dose related adverse effects as well as no effect levels. Considerable variability was encountered in the biological endpoints used to define NOAEL values which ranged from gross effects such as mortality to more subtle changes in biochemical, physiological, or pathological parameters.

The NOAEL was transformed into an Acceptable Daily Intake for man (ADI) by dividing by an uncertainty factor of 10, 100, or 1000. The guidelines for using the uncertainty factors, as given by the National Academy of Sciences (26), are outlined below:

1. Valid experimental results from studies on prolonged ingestion by man, with no indication of carcinogenicity: Uncertainty Factor = 10
2. Experimental results of studies of human ingestion not available or scanty (e.g., acute exposure only); valid results of long-term feeding studies on experimental animals or in the absence of human studies, valid animal studies on one or more species; no indication of carcinogenicity: Uncertainty Factor = 100
3. No long-term or acute human data; Scanty results on experimental animals; no indication of carcinogenicity: Uncertainty Factor = 1000
For a few of the chemicals or chemical classes, ADI values were estimated from threshold limit values (TLV) or subacute/acute mammalian data. The TLV values are established by the ACGIH and represent estimated levels of the compounds in the work environment which are not anticipated to result in significant adverse health effects in workers exposed 8 hours/day, 5 days/week. The method used to derive the ADI from TLV is essentially that recommended by Stokinger and Woodward (56) and is based on assumptions of the breathing rate and completeness of absorption.

Once an ADI is established, assumptions are made concerning the relative contribution of water to total human exposure. Criteria are calculated in a manner analogous to that used in carcinogenicity studies:

\[ C = \frac{\text{ADI}}{\text{WC}} + (RF) \]

For all compounds, criteria used were based on an assumed daily water consumption of 2 liters.

**Examples of Proposed Criteria**

Based on the previously described methodology for health risk assessment, criteria for ambient water can be derived as long as a sufficient data base exists. Examples of the derived criteria are presented in Tables 2-7 and are based on the different methods used in the treatment of the data which provide the basis for evaluation of effects. The presented examples of criteria levels are preliminary and designed to inform the reader of the approaches used. Public review of the documents is underway, and, based on the public comments, it is likely that many of the proposed criteria will be revised. In addition to the criteria, each table lists existing standards, references of studies used for criterion derivation, and the estimated bioconcentration factor in aquatic organisms.

In Table 2 criteria for arsenic and benzene have been derived directly from available human carcinogenic data (57-60). Neither compound has been shown to produce carcinogenic response in experimental animals. The criterion for vinyl chloride has been derived from the carcinogenic data on mice and rats (61) by using the linear (one-hit) model and correlated with reported human occupational exposure on the incidence of hemangiosarcoma (62-65). Vinyl chloride does not appear to be of significance in water media with the exception of effluents from vinyl chloride and poly(vinyl chloride) plants.

Table 3 summarizes several criteria for heavy metals where the data base used for criterion derivation was chronic toxicity in the case of cadmium (66-68), lead (69, 70), nickel (71), chromium (72), and thallium (73) and organoleptic effect in the case of copper (74) and zinc.

Table 4 lists three chemicals (hexachlorocyclopentadiene, acenaphthene, and 2-chlorophenol) for which the basis for criterion derivation was organoleptic, i.e., taste and odor (75-77). This approach was used either because the organoleptic effects in humans resulted in a lower criterion than available toxicity data, as was the case for hexachlorocyclopentadiene, or insufficient toxicity data were available in the literature and taste and odor studies had to be used.

The chemical compounds listed in Table 5 represent examples of criteria derived from carcinogenic responses in experimental animals. In these instances, animal carcinogenic bioassay data were used for the derivation of water quality criteria. Of particular interest is the variability of the bioconcentration factor in aquatic organisms which affects the final calculated number. Since the exposure factors used are based on the consumption of two liters of water daily and 18.7 g of contaminated fish products, any bioconcentration factor above about 100 lowers the final calculation substantially. In the case of tetrachloroethylene which bioconcentrates in the edible portion of fish 110 times, the contribution of the fish products to the total exposure is about 50% (2000 ml water vs. 18.7 g × 110 ml/g = 2057 ml water equivalent). In the case of heptachlor and DDT, the ingestion of contaminated fish products completely overshadows the contribution of the exposure from ingested water.

**Examples of criteria based on chronic toxicity**

**Table 2. Criteria based on carcinogenic response: human data**

| Substance      | External standard | Basis                        | BCF  | Criterion     | Reference |
|----------------|-------------------|------------------------------|------|---------------|-----------|
| Arsenic        | OSHA (airborne):  | Skin cancer, man (lifetime)  | 1.0  | 0.02 µg/l.   | (57)      |
|                | 10 µg/m³          |                              |      |               |           |
|                | TLV: 0.5 mg/m³    |                              |      |               |           |
| Benzene        |                   | Leukemia, man                | 6.9  | 15 µg/l.     | (58-60)   |
| Vinyl chloride | 1 ppm             | Hemangiosarcoma, man, mice, rats | 1.9  | 517 µg/l.    | (62-65)   |
|                |                   |                              |      |               | (61)      |
Table 3. Criteria for heavy metals

| Substance   | External standard | Basis                                      | BCF | Criterion      | Reference |
|-------------|-------------------|--------------------------------------------|-----|----------------|-----------|
| Cadmium     | EPA, FDA, WHO: 10 µg/l. | Toxicity, chronic human data               | 17  | 10 µg/l.       | (66-68)   |
| Lead        | EPA: 50 µg/l.      | Blood lead levels (chronic human data)     | N.U.| 50 µg/l.       | (69, 70)  |
| Nickel      | None              | Toxicity, chronic animal data              | N.U.| 133 µg/l.      | (71)      |
| Chromium    | US PHS: 50 µg/l.   | Toxicity, chronic animal data              |     | 50 µg/l.       | (72)      |
| Thallium    | TLV: 0.1 mg/m³    | Toxicity, chronic animal data              | 61  | 4 µg/l.        | (73)      |
| Copper      | NIOSH (air): 1 mg/m³ (dust) 0.2 mg/m³ (fumes) NIOSH (water): 1 mg/l. 5 mg/l. | Organoleptic                |     | 1 mg/l.       | (74)      |
| Zinc        |                   | Organoleptic                               | N.U.| 5 mg/l.        |           |

Table 4. Criteria based on organoleptic effects

| Substance               | External standard | Basis                  | BCF | Criterion      | Reference |
|-------------------------|-------------------|------------------------|-----|----------------|-----------|
| Hexachlorocyclopentadiene | TLV: 0.11 mg/m³  | Organoleptic           | 3.2 | 1.0 µg/l.      | (75)      |
|                        | STEL: 0.33 mg/m³ |                        |     |                |           |
| Acenaphthene            | None              | Organoleptic           | 890 | 20 µg/l.       | (76)      |
| 2-Chlorophenol          | None              | Organoleptic           |     | 0.3 µg/l.      | (77, 78)  |

Table 5. Criteria based on carcinogenic response: animal data

| Substance                | External standard | Basis                                                                 | BCF  | Criterion      | Reference |
|--------------------------|-------------------|------------------------------------------------------------------------|------|----------------|-----------|
| 2,4-Dinitrotoluene       | TLV-TWA: 1.5 mg/m³| Fibroadenomas of the subcutaneous ulcerated tissue and inanition, rats | 5.5  | 0.74 µg/l.     | (79)      |
| Chloroform               | NIOSH: 2 ppm      | Hepatocellular carcinomas, mice                                        | 14   | 2.1 µg/l.      | (80)      |
| Carbon tetrachloride     | USA: 670 mg/m³    | Liver tumors, mice                                                     | 69   | 2.6 µg/l.      | (81)      |
|                         | USSR: 1 mg/m³     |                                                                        |      |                |           |
| Tetrachloroethylene      | USA: 670 mg/m³    | Hepatocellular carcinoma, mice                                         | 110  | 2.2 µg/l.      | (82)      |
|                         | USSR: 1 mg/m³     |                                                                        |      |                |           |
| Heptachlor               | OSHA: 500 µg/m³   | Liver carcinoma, mice                                                  | 5,200| 0.23 µg/l.     | (83)      |
|                         | USSR: 1 mg/m³     |                                                                        |      |                |           |
|                         | NAS: 4. x 10⁻⁴ µg/l. (lifetime cancer risk)                           |      |                |           |
| DDT                     | OSHA: 1 mg/m³ (skin) | Liver tumors, mice                                                   | 39,000 | 9.8 x 10⁻⁷ mg/l. | (84)      |
|                         | EPA: 0.001 µg/l. (water) |                                                                   |      |                |           |
|                         | WHO: 0.005 mg/kg (ADI)    |                                                                      |      |                |           |

Data using the threshold assumption are listed in Table 6. For ethylbenzene and chlorinated naphthalenes, Threshold Limit Values (TLV) were used, since the literature reports did not contain adequate studies on chronic toxic effects following ingestion. The Stockinger and Woodward model was used as shown in Table 7 with appropriate safety factors added as recommended by the NAS publication (26). For some compounds, the scientific review committees were unable to discover sufficient data from which a criterion could be calculated. In those cases criteria were not proposed. Examples of these chemicals are 2,4-dimethylphenol, antimony, chloromethyl methyl ether, and the δ and ε isomers of hexachlorocyclohexane.

The chemicals listed in Tables 2-7 are examples of...
a large number of compounds presently under review by the EPA’s water quality office. Fortunately, we were able to secure the services of a large number of experts who assisted in drafting the assessment documents and in providing peer review for each chapter. It is hoped that these documents will be of use to the scientific community, industry, and regulatory agencies.

**Summary and Conclusions**

Hazard assessment is an inexact process which requires judgement at the scientific level and careful public policy decision-making. In this paper, we have merely attempted to review some of the factors which must be considered in hazard assessment, discuss some of the problems in this process, and describe the methodology currently being used by the EPA in setting water quality criteria based on human health effects.

Many problems and questions remain. Our current approach is hopefully reasonable but may and probably will require additional reviews and refinements. This approach may serve as a foundation upon which a more valid system can be developed as the relevant information and methods of interpreting this information improve. If nothing else, the approach may serve as a convenient target, stimulating constructive debate and eliciting alternative solutions. It is imperative that the solutions are sought and found by the scientific community. They will affect not only public health but also the quality of our life.

**REFERENCES**

1. Murdoch, W. W., Ed. Environment, 2nd ed., Sinauer Associates, Inc. Sunderland, Mass., 1975.
2. van der Leeden, F., Ed. Water Resources of the World, Water Information Center, Inc., Port Washington, N.Y., 1975.
3. van Hylckama, T. E. A. Water resources. In: Environment, W. W. Murdoch, Ed., Sinauer Associates, Inc. Sunderland, Mass., 1975, p. 147.
4. Fraser, D. The People Problem. Indiana University Press, 1971.
5. Statistical Abstract of the United States. U.S. Department of Commerce, Bureau of the Census, 1975.
6. Doxiadis, C. A. Water and Environment. International Conference on Water for Peace, Washington, D.C., 1967.
7. Council on Environmental Quality. Environmental Quality (9th Ann. Rept. of the Council on Environmental Quality), Washington, D.C., 1978.
8. U.S. Environmental Protection Agency. National Water Quality Inventory: 1977 Report to Congress, U.S. Government Printing Office, Washington, D.C., 1978.
9. Middleton, F. A., and Rosen, A. A. Organic contaminants affecting the quality of water. Public Health Repts. 71: 1125 (1956).
10. Hueter, W. C., and Conway, W. D. Chemical Carcinogens and Cancers. Charles C Thomas, Springfield, Ill., 1964.
11. Harris, R. H., Page, T., and Reiches, N. A. Carcinogenic hazards of organic chemicals in drinking water. In: Origins of Human Cancer, H. H. Hiatt, J. S. Watson, and J. A. Winsten, Eds., Cold Spring Harbor Laboratory, 1977.
12. Jolley, R. L. Chlorination Effects on Organic Constituents in Effluents from Domestic Sanitary Sewage Treatment Plants. Publication No. 565, Environmental Science Division, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1973.
13. Harris, R. H. Implications of Cancer-Causing Substances in Mississippi River Water. Environmental Defense Fund, Washington, D.C., 1974.
14. U.S. Environmental Protection Agency. Industrial Pollution
of the Lower Mississippi River in Louisiana. EPA, Dallas, Texas, 1972.

15. Kleopfer, R. D., and Fairless, B. J. Characterization of organic components in a municipal water supply. Environ. Sci. Technol. 6: 1036 (1972).

16. Deinzer, M., et al. Trace Organic Contaminants in Drinking Water: Their Concentration by Reverse Osmosis. Environmental Protection Agency, Cincinnati, Ohio, 1974.

17. Scheiman, M. A., Saunders, R. A., and Salfeld, F. E. Organic contaminants in the District of Columbia water supply. Bio. Mass. Spec. 1: 209 (1974).

18. Junk, G. A., and Stanley, S. E. Organics in Drinking Water. Part I. Listing of Identified Chemicals. National Technical Information Service, Springfield, Va., 1975.

19. Buncher, C. R., Kuzma, R. J., and Forcade, C. M. Drinking water as an epidemiologic risk factor for cancer. In: Origins of Human Cancer, H. H. Hiatt, J. S. Watson, and J. A. Winsten, Eds., Cold Spring Harbor Laboratory, 1977.

20. DeRouen, T. A., and Diem, J. E. Relationships between cancer mortality in Louisiana drinking-water source and other possible causative agents. In: Origins of Human Cancer, H. H. Hiatt, J. S. Watson, and J. A. Winsten, Eds., Cold Spring Harbor Laboratory, 1977.

21. Maugh, T. H., II. Chemicals: How many are there? Science 199: 162 (1978).

22. Kraybill, H. F. Global distribution of carcinogenic pollutants in water. Ann. N. Y. Acad. Sci. 298: 80 (1977).

23. Howard, P., Santodonato, J., and Durkin, P. Syracuse research corporation approach to chemical hazard assessment. In: Environmental Risk Analysis for Chemicals, R. A. Conway, Ed., Van Nostrand Reinhold Co., New York, 1979, in press.

24. Rall, D. P. Difficulties in extrapolating the results of toxicity studies in laboratory animals to man. Environ. Res. 2:360 (1969).

25. Stara, J. F., and Kello, D. Relationship of long-term animal studies to human disease. In: Assessing Toxic Effects of Environmental Pollutants, S. D. Lee, and J. B. Mudd, Eds., Ann Arbor Science, Ann Arbor, Michigan, 1979.

26. NAS. Drinking Water and Health. National Academy of Sciences, Washington, D.C., 1977.

27. Water Quality Criteria. Federal Register 44: 15926 (1979).

28. Cordie, F., et al. Human exposure to polychlorinated biphenyls and polybrominated biphenyls. Environ. Health Perspect. 24: 157 (1978).

29. The Scientific Committee, Food Safety Council. Proposed system for food safety assessment. Food Cosmet. Toxicol. 16:1 (1978).

30. Gehring, P. J., Watanabe, P. G., and Blau, G. E. Pharmacokinetic studies in evaluation of the toxicological and environmental hazard of chemicals. In: Advances in Modern Toxicology, Vol. 1, Part 1, M. A. Mehlman, R. E. Shapiro, and H. Blumenthal, Eds., Hemisphere Publishing Co., Washington, D.C., 1976.

31. Dominguez, G. Guidebook: Toxic Substances Control Act. CRC Press, Cleveland, Ohio, 1977.

32. Toxic Substances Control Act. October 11, 1976.

33. Well, C. S. Guidelines for experiments to predict the degree of safety of a material for man. Toxicol. Appl. Pharmacol. 21: 194 (1972).

34. McNamara, B. P. Concepts in health evaluation of commercial and industrial chemicals. In: Advances in Modern Toxicology, Vol. 1, Part 1, M. A. Mehlman, R. E. Shapiro, and H. Blumenthal, Eds., Hemisphere Publishing Co., Washington, D.C., 1976.

35. Friedman, L. Symposium on the evaluation of the safety of food additives and chemical residues: II. The role of the laboratory animal study of intermediate duration for evaluation of safety. Toxicol. Appl. Pharmacol. 16: 498 (1970).

36. Lenz, W. Kindliche Missbildungen nach Medikament während der Gravidität? Deutsch. Med. Wochenschr. 86: 2555 (1961).

37. McBride, W. G. Thalidomide and congenital abnormalities. Lancet 2:1358 (1961).

38. Kimmel, C. A., and Wilson, J. G. Skeletal deviations in rats: malformations or variations? Teratology 8:309 (1973).

39. Infante, P. F., and Legator, M., Eds., Workshop on Methodology for Assessing Reproductive Hazard in the Workplace. NIOSH, DHED Publication, in press.

40. Weil, C. S. Selection of the valid number of sampling units and a consideration of their combination in toxicological studies involving reproduction, teratogenesis or carcinogenesis. Food Cosmet. Toxicol. 8:177 (1970).

41. Collins, T. F. X., and Collins, E. V. Current methodology in teratology research. In: Advances in Modern Toxicology, Vol. 1, Part 1, M. A. Mehlman, R. E. Shapiro, and H. Blu- mentalh, Eds., Hemisphere Publishing Co., Washington, D.C., 1976.

42. McCann, J., Choi, E., Yamasaki, E., and Ames, B. N. Detection of carcinogens as mutagens in the Salmononella/ microsome test. Assay of 300 chemicals. Proc. Natl. Acad. Sci. (U.S.) 72:5135 (1975).

43. Interagency Regulatory Liaison Group. Scientific bases for identifying potential carcinogens and estimating their risk. Feb. 6, 1979.

44. Albert, R. E., Train, R. E., and Anderson, E. Rationale developed by the Environmental Protection Agency for the assessment of carcinogenic risks. J. Natl. Cancer Inst. 58: 1537 (1977).

45. National Cancer Advisory Board. General criteria for assessing the evidence for carcinogenicity of chemical substances: Report of the Subcommittee on Environmental Carcinogens, National Cancer Advisory Board. J. Natl. Cancer Inst. 58:461 (1977).

46. Webster's New Collegiate Dictionary. G. & C. Merriam Company, Springfield, Mass., 1975.

47. Gehring, P. J., and Blau, G. E. Mechanisms of carcinogenesis: dose response. J. Environ. Pathol. Toxicol. 1: 163 (1977).

48. Maugh, T. H., II. Chemical carcinogens: how dangerous are low doses? Science 202: 37 (1978).

49. Jones, H. B., and Grendon, A. Environmental factors in the origin of cancer and estimation of the possible hazard to man. Food Cosmet. Toxicol. 13: 251 (1975).

50. Clayson, D. B. Chemical carcinogenesis: dose-response extrapolation. Science 203: 1068 (1979).

51. Hooper, N. K., Harris, R. H., and Ames, B. N. Chemical carcinogens. Science 203: 602 (1979).

52. Schneiderman, M. A. Letter. Science 203:603 (1979).

53. Weigert, F. J. Letter, Science 203: 603 (1979).

54. Anon. Agency's interim cancer procedures and guidelines for health risk and economic impact assessments of suspect carcinogens. Federal Register 41:21402 (1976).

55. Sidwell, V. D., et al. Composition of the edible portion of raw crustaceans, finfish, and molluscs. Marine Fisheries Rev. 36: 21 (1974).

56. Stokinger, M. E., and Woodward, R. L. Toxicologic methods for establishing drinking water standards. J. Am. Water Works Assoc. 50: 571 (1958).

57. Tseng, W. P., et al. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J. Natl. Cancer Inst. 40: 453 (1968).

58. Aksoy, M., Erdem, S., and Dincol, G. Leukemia in shoe-workers exposed chronically to benzene. Blood 44:837 (1974).

59. Infante, P. F., et al. Leukemia in benzene workers. Lancet 2:76 (1977).

60. Ott, M. G., et al. Mortality among individuals occupationally
exposed to benzene. Arch. Environ. Health 33: 3 (1978).
61. Maltoni, C., and Lefemine, G. Carcinogenicity bioassays of vinyl chloride: current results. Ann. N.Y. Acad. Sci. 246: 195 (1975).
62. Ott, M. G., Langner, R. R., and Holder, B. B. Vinyl chloride exposure in a controlled industrial environment. Arch. Environ. Health 30:333 (1975).
63. Tabershaw, J. R., and Gaffey, W. R. Mortality study of workers in the manufacture of vinyl chloride and its polymers. J. Occup. Med. 16: 509 (1974).
64. Nicholson, W. J., et al. Mortality experience of a cohort of vinyl chloride — polyvinyl chloride workers. Ann. N.Y. Acad. Sci. 246: 225 (1975).
65. Heath, C. W., Jr., Falk, H., and Creech, G. L., Jr. Characteristics of cases of angiosarcoma of the liver among vinyl chloride workers in the United States. Ann. N.Y. Acad. Sci. 246: 231 (1975).
66. Friberg, L., et al. Cadmium in the Environment. 2nd ed., CRC Press, Cleveland, Ohio, 1974.
67. Nordberg, F. G. Effects and Dose-Response Relationship of Toxic Metals. Elsevier, Amsterdam, 1976.
68. U.S. EPA. Review of the Environmental Effects of Pollutants: IV. Cadmium. EPA-600/1-78-026, 1978.
69. Moore, M. R., et al. Contribution of lead in drinking water to blood-lead. Lancet 2:661 (1977).
70. Hubermont, G., et al. Placental transfer of lead, mercury, and cadmium in women living in a rural area. Int. Arch. Occup. Environ. Health 41: 117 (1978).
71. Schroeder, H. A., and Mitchener, M. Toxic effects of trace elements on the reproduction of mice and rats. Arch. Environ. Health 23:102 (1972).
72. U.S. Public Health Service. PHS Publication No. 956, 1962.
73. Downs, W. L., et al. Acute and subacute toxicity studies of thallium compounds. Am. Ind. Hyg. Assoc. J. 21: 399 (1960).
74. U.S. Department of Health, Education and Welfare. Community Water Supply Study. Significance of National Findings. Public Health Service Environmental Health Service, Bulletin of Water Hygiene, Washington, D.C., 1970, p. 13.
75. Naishstein, S. Y. U., and Lisovskaya, E. V. Maximum permissible concentration of hexachlorocyclopentadiene in water bodies. Gig. Sanitar. 30: 177 (1965).
76. Lillard, D. A., and Powers, J. J. Aqueneous odor thresholds of organic pollutants in industrial effluents. EPA Rept. No. EPA-660/4-75-002 National Environmental Research Center, ORD, U.S. EPA, Corvallis, Ore., 1975.
77. Burtschell, R. H., et al. Chlorine derivatives of phenol causing taste and odor. J. Am. Water Works Assoc. 51: 205 (1959).
78. Hoak, R. D. The causes of tastes and odors in drinking water. Water Sewage Works 104: 243 (1957).
79. Lee, C. C., et al. Mammalian toxicity of munition compounds. Phase III: Effects of lifetime exposure. Part I: 2,4-Dinitrotoluene. U.S. Army Medical Research and Development Command Contract No. DAMD-17-74-C-4073 Report No. 7, September 1978.
80. National Cancer Institute. Report on carcinogenesis bioassay of chloroform. Natl. Tech. Inf. Serv. PB-264018 Springfield, Va. 1976.
81. National Cancer Institute. Carcinogenesis bioassay of trichloroethylene, CAS No. 79-01-6. NCI-CG-TR-2. U.S. DHEW, 1976.
82. National Cancer Institute. Bioassay of tetrachloroethylene for possible carcinogenicity, CAS No. 127-18-4. NCI-CG-TR-13. U.S. DHEW Pub. No. (NIH) 77-813, 1977.
83. Davis, K. J. Pathology report on mice fed aldrin, dieldrin, heptachlor, or heptachlor epoxide for two years. Internal memorandum to Dr. A. J. Lehman. U.S. Food Drug Administration, 1965.
84. Turowski, V. S., et al. Tumors in CF-1 mice exposed for six consecutive generations to DDT. J. Natl. Cancer Inst. 51: 983 (1973).
85. Schwartz, B. A., et al. Results of two year toxicity and reproduction studies on pentachlorophenol in rats. In: Pentachlorophenol: Chemistry, Pharmacology and Environmental Toxicology, K. R. Rao, Ed., Plenum Press, New York, 1978.
86. National Cancer Institute. Bioassay of endosulfan for possible carcinogenicity. National Cancer Institute Division of Cancer Cause and Prevention, National Institutes of Health, Public Health Service, U.S. Department of Health, Education and Welfare, Bethesda, Maryland, Pub. 78-1312; Report by Hazleton Laboratories to NCI, NCI-CG-TR-62, 1978, p. 54.
87. Wolf, M. A., et al. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health 14:387 (1956).
88. American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values for substances in workroom air. Cincinnati, Ohio, 1971.