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November 19, 1974

To: Technical Task Group on Vinyl Chloride Research

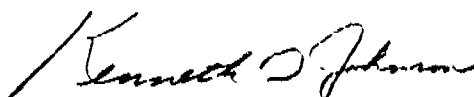
Subject: Draft of EPA Briefing Report Environmental Aspects
of Vinyl/Polyvinyl Chloride

Gentlemen:

Today I secured a copy of the subject draft (about 235 pages) dated October 15, 1974. Much of this copy is not of quality suitable for reproduction, but the title page, preface, table of contents, the summary and conclusions and the chapter on Biological and Statistical Consideration in the Assessment of Risk have been reproduced, and are distributed herewith.

The file copy of the full text will be available for review at MCA offices.

Sincerely,



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BRIEFING REPORT

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External Review Draft

ENVIRONMENTAL ASPECTS OF
VINYL/POLYVINYL CHLORIDE

NOTICE

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be considered to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.

U.S. ENVIRONMENTAL PROTECTION AGENCY
NATIONAL ENVIRONMENTAL RESEARCH CENTER
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October 15, 1974

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PREFACE

This report was prepared by a Task Force convened under the direction of Dr. John F. Finklea, Director, National Environmental Research Center (NERC) in June, 1974. In a preliminary assessment of the environmental problems associated with vinyl chloride and polyvinyl chloride, an EPA Task Force under the direction of the Office of Toxic Substances determined that emissions of vinyl chloride monomer was primarily an air pollution problem. Accordingly, the Office of Air and Solid Waste was given the responsibility for an in-depth evaluation of the problem. This report was proposed as a part of this evaluation. The objective was to review and evaluate the current knowledge of vinyl chloride and polyvinyl chloride emissions into the environment as related to possible deleterious effects upon human health and welfare.

The units of parts per million (ppm), in lieu of metric units, have been used in this report to be consistent with other agencies currently involved in the national assessment of the vinyl chloride problem.

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1. *Chlorophyll a* (Chl *a*)

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1. SUMMARY AND CONCLUSIONS

1.1 SUMMARY

This report represents a review and evaluation of the available current scientific data relative to the health and welfare implications of environmental pollution resulting from the production and use of vinyl chloride and polyvinyl chloride. New information about this compound has become available and important new data may be forthcoming in the near future.

Vinyl chloride monomer (VCM) was first synthesized in 1837. The vinyl chloride monomer is a synthetic chemical derived from petrochemical feedstock and chlorine. Its principal use is in the production of a wide variety of useful plastic materials such as floor tile, phonograph records, pipes and electrical insulation, although it has also been used in other ways, for example, as an aerosol propellant. The production of vinyl chloride began in the United States in the 1930's, the first important use was in the manufacture of synthetic rubber. Production levels increased rapidly after World War II--the beginning of the industrial chemical era which has produced over 20,000 new chemical products. Vinyl chloride production in the U.S. was less than 45 million kilograms (kg) in 1943 but exceeded 2.9 billion kg in 1973. The annual growth rate in this industry is expected to exceed 10 percent per year through the 1980's. In the United States vinyl chloride monomer is produced at 15 plants and polyvinyl chloride (PVC) is produced at 37 plants.

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Approximately 1500 workers are engaged in the production of vinyl chloride, and approximately 5000 are engaged in the production of polyvinyl chloride. The demand for products and components manufactured from polyvinyl chloride is extensive due to its widespread use,

thus the impact of control actions will be felt beyond the VCM/PVC industry. Thousands of companies, large and small, and hundreds of thousands of workers are engaged in the manufacture of and/or use of plastic products made from PVC.

Only a very limited amount of VCM emission data from industrial sources is available. VCM loss estimates of approximately 6 percent have been reported, based primarily on material balance studies. Losses to the outdoor atmospheres from industrial sources may occur at a large number of points in the manufacturing processes and will vary depending upon the manufacturing facility.

Currently, emissions of vinyl chloride from VCM and PVC plants are estimated to exceed 90 million kg annually. It is estimated that 90 percent of all vinyl chloride atmospheric emissions are believed to emanate from polyvinyl chloride plants. Monomer plants emit less than 10 percent of the total. Emissions of VCM from fabricating plants and from fabricated products may also occur, but at present there are no data to quantify what those emissions may be. The concentration of residual monomer in PVC powder that is fabricated into final products is an important determinant of VCM emissions in both these cases. Fugitive emissions contribute a significant fraction to total VCM emissions, particularly in PVC plants, and these emissions are an important limiting factor in determining the degree of emissions control that can be achieved.

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Technology may currently be available to reduce vinyl chloride emissions from VCM plants by as much as 90 percent and from PVC plants by as much as 75 percent. Control of emissions from PVC plants is a more difficult problem which may require complex process changes. Means of controlling emissions from PVC plants and from fabrication processes are yet to be determined.

Polyvinyl chloride plastics usually are not readily biodegradable. Incineration (without scrubbing) of polyvinyl chloride plastics results in the emission of hydrogen chloride gas, but not VCM. Experimental studies indicate that vegetational injury symptoms for ethylene and vinyl chloride are identical, however, no known information showing vegetational damage around VCM manufacturing or processing plants exists.

Vinyl chloride is a chlorinated olefinic hydrocarbon monomer which is a gas at ambient temperatures and atmospheric pressure. It is normally shipped and stored as a liquid under pressure. It is flammable, explosive, and only slightly soluble in water. VCM is about two times heavier than air. Analysis of vinyl chloride usually reveals trace amounts of organic impurities, such as acetylene, 1,3-butadiene, methyl chloride, vinylidene, and vinyl acetate. Polyvinyl chloride contains residual entrapped VCM in the parts per million range. The entrapped concentration is dependent upon the production process and can range from 0.1 to several (5-8) thousand ppm, which can be liberated during fabrication, particularly when heated. The production of VCM/PVC involves the use of a wide variety of chemicals other than VCM which also may contribute to adverse health effects under occupational circumstances.

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There are few data on exposure levels of vinyl chloride in ambient air. The work place peak exposures in the past may at times have exceeded thousands of ppm; however, the average concentration would have been less. Limited atmospheric vinyl chloride concentration measurements have been made in the vicinity [0 to 8 kilometers (km)] of VCM/PVC production sources. In over 90 percent of the cases the peak concentrations have been below 1 ppm; however, one peak value (grab sample) of 33 ppm has been observed. A few twenty-four-hour average values of 1 to 3 ppm, at distances of 0.8 to 8 km from the source, have also been measured, probably in the downwind plume, although over 90 percent of 24-hour measurements were below 1 ppm.

Because of the sampling and analytical procedures used, the accuracy of these measurements may be no better than $\pm 100\%$.

Available atmospheric VCM data have been obtained using a variety of sampling and analytical techniques with varying degrees of sensitivity and accuracy. Consequently, the data are not directly comparable. Standard sampling and analytical procedures have not been established and practiced. Continuous monitoring methods suitable for field use are not available. Measurement methodology is inadequate, but has not yet been applied to the problem of atmospheric and source sampling for VCM. The nature of VCM/PVC manufacturing facilities, particularly the older plants, is such that conventional source monitoring techniques may not be applicable due to the discontinuous nature of emissions. Using an atmospheric

dispersion model, estimates of VCM concentration in a downwind plume indicate that hourly integrated concentrations of 1 to 30 npp might be expected depending upon atmospheric wind and stability conditions. The measured values and the values predicted by the model are the same order of magnitude.

Only limited laboratory studies have been made regarding photochemical reactions of VCM. Vinyl chloride does undergo atmospheric reactions in the presence of nitrogen oxides and solar radiation; although the reaction rate is slower than with other hydrocarbons known to be in the atmosphere. Reaction products of VCM photooxidation include CO, formaldehyde, formic acid, formyl chloride and hydrogen chloride. In addition, VC may indirectly contribute to the buildup of ozone. The extent to which VCM contributes to these other components in photochemical smog is not known. The estimated half-life of VCM in the atmosphere is about 6 hours.

The principle route of human exposure to vinyl chloride is thought to be through air inhalation, although exposure could occur from ingestion of food and water, and from skin contact. There is no evidence to indicate that vinyl chloride exists in normal drinking water, or in foods, except possibly in special cases involving leaching of VCM from wrapping and storage materials. Use of vinyl chloride as a propellant in aerosol products has also recently been discontinued so that this source of exposure, though significant in past years, is not anticipated to represent a problem in the future.

Acute animal toxicity to VCM was first reported in 1938. Toxic manifestations in experimental animals and man included eye irritation, increased motor activity leading to tremor and loss of muscular

coordination, and finally narcosis, and cardiac irregularities. Exposure concentrations in these acute studies ranged up to 400,000 ppm for periods extending from 30 minutes to daily exposure of several hours.

Short-term acute human experiments (intermittent 5 minute exposures separated by 6 hours over a period of 3 days) with concentrations ranging up to 20,000 ppm produced acute toxic effects at levels above 8,000 ppm.

Chronic toxicity effects due to VCM in experimental animals include cancer, damage to the liver, spleen, kidney, lungs, brain and nerve bundles.

Some of the pathological lesions observed in these animal experiments were similar to those later observed in humans engaged in the production and handling of vinyl chloride.

Our present knowledge of undesirable health effects associated with vinyl chloride exposure in man comes primarily from recent occupational observations, complemented by additional animal data. Between 1949 and 1966 an increased incidence of excessive liver damage and acroosteolysis, a degenerative disease affecting bones and fingertips were reported among vinyl chloride workers in Europe. Studies in Germany revealed evidence of liver pathology in an abnormally high percentage of PVC production workers with a history of employment ranging from 1.5 to 21 years, but exposure levels responsible for this damage are not known. Since early occupational health studies often reported acute toxic effects, similar to those found in the human experiments previously mentioned (dizziness, headaches, nausea, etc.), it can be assumed that peak exposure levels of several thousand ppm were experienced at times.

Available air monitoring data in PVC plants during the period 1950-1959 indicates that the highest time weighted average exposures in these facilities were in the range 120-385 ppm. Studies in Europe

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and the United States since 1966 tend to confirm the earlier findings in Europe. These studies include observations of liver damage among workers not directly involved in the actual production of PVC. The frequency and severity of liver pathology among PVC workers has been related to the length of exposure; i.e. being most common in workers with an exposure history in excess of 10 years. In one study, the degree of damage did not appear to decrease with increasing intervals of time between the last exposure and taking of biopsies.

To date 15 cases of liver angiosarcoma have been reported among workers with a history of exposure to vinyl chloride in the United States and 10 such cases have been reported from Europe. Most, but not all, of these reported cases have been among workers involved directly in PVC production. Cases of liver angiosarcoma have been reported in 1 U.S. and 3 European workers exposed to VCM, but not directly involved in PVC production. These cases suggest that exposure to vinyl chloride at lower levels than usually encountered in PVC production plants may be capable of causing liver angiosarcoma. Two community cases of liver angiosarcoma have also been reported in persons whose residences were in the vicinity of industrial VCM emission sources, which raises the question as to whether or not ambient air levels of VCM may, under certain circumstances, contribute to this disease. Additional studies are, however, necessary to confirm this possibility. Based upon the present reporting methods, angiosarcoma is a rare form of liver cancer in the general population, and for all practical purposes, is invariably fatal. The latent period for liver

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Angiosarcoma has been estimated at about 20 years, based upon medical and occupational exposure cases. The levels and durations of exposure necessary to induce liver angiosarcoma in the occupational or the general population living in the vicinity of emissions sources are not precisely known.

Compared to the general population, the relative risk of liver angiosarcoma among workers exposed in the past to high levels of vinyl chloride is estimated at approximately 3,000. Such a relative risk represents a striking statistically significant difference ($p < 0.01$) in the frequency of liver angiosarcoma among those exposed to high levels of vinyl chloride compared to those in the general population not exposed or exposed to much lower levels.

While the focus of attention has been on liver angiosarcoma, it should be noted that a number of industrial studies indicate that the risk of developing other cancers besides liver angiosarcoma, particularly lung and brain cancer, is also related to exposure to vinyl chloride. The multiple cancer risk associated with vinyl chloride also is supported by the available animal studies.

Chronic toxic effects of VCM have been studied in a variety of animal species. Angiosarcoma of the liver has been observed in rats, hamsters, and mice exposed to vinyl chloride. Angiosarcoma was not observed in all animal studies. In all of these, rats and mice, liver angiosarcoma has been produced by exposures as low as 50 ppm. The frequency of liver angiosarcoma in experimental animals appears to be dose-dependent above 50 ppm, but the shape of the dose-response curve below 50 ppm is not known. Duration of exposure has been shown to affect the tumor response in animals. Other damage,

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including tumors of the lung, spleen, and kidneys has been observed in animals exposed to vinyl chloride,

VCM/PVC workers are exposed to a variety of chemicals which may be carcinogens and/or liver toxins in addition to VCM. Such a complex exposure pattern makes it difficult to draw final conclusions regarding the specific role played by vinyl chloride in the development of liver cancer. However, the results of animal experiments demonstrating liver angiosarcoma from exposure to VCM in 3 species, coupled with occupational data

implies that vinyl chloride is a causal factor in the development of liver angiosarcoma.

Although actual VCM exposure levels responsible for liver angiosarcoma and/or other cancers in man are not precisely known, limited measurements around VCM/PVC production facilities indicate that contiguous populations are being exposed to low levels of vinyl chloride, which may impose a health risk.

The presence or importance of chemical co-factors besides vinyl chloride in the etiology of liver angiosarcoma is not well defined, though other chemicals thorotrast and besides VCM; i.e./arsenicals have been associated with liver angiosarcoma in man. Health implications relating to PVC dust particles containing well residual VCM have not been studied.

Data in animals and man for the lower end, less than 50 ppm, of the VCM dose response curve are not available. Attempts to extrapolate animal dose response curves to define a presumed "no-effect" level are fraught

with problems which impact upon the state-of-the art in cancer research, and the availability of resources required to conduct long time chronic studies. Similarly it is difficult to extrapolate data in experimental animals directly to man who may be more or less sensitive than animals to given chemical structures. These problems reflect important gaps in our knowledge concerning environmentally related cancers.

The mechanism for producing liver angiosarcoma by the inhalation of VC has been postulated but has not been confirmed. It is also not known whether the mechanism can be activated by intermittent peak exposures or whether frequent, or essentially continuous, exposure to low concentrations is sufficient to cause cancers to develop.

1.2 CONCLUSIONS

Precise data that indicate the degree to which the general population is exposed to vinyl chloride, and its consequent effects, are not available. However, available data supports the following tentative conclusions:

1. Vinyl chloride in the atmosphere in the vicinity of emission sources is a potential health hazard.
2. Occupational cases of angiosarcoma have been observed among PVC production workers predominantly with long-term exposure (greater than 20 years) to VCM at unknown, but suspected high, concentrations. However, cases of liver angiosarcoma have been reported among workers exposed to VCM but not directly involved in PVC production, raising the question of effects at lower levels of exposure.
3. Observations among workers and in experimental animals indicate that there is a multiple cancer risk from exposure to vinyl chloride.

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and liver angiosarcoma and other

4. The mechanism and dose-response relationships between vinyl chloride/ at community exposure levels are not known.

5. Persons living in the immediate vicinity of VCM/PVC plants have been exposed an unknown number of times to 24-hour average concentrations of VCM of at least 1 ppm with occasional peak exposures of 30 ppm, however, over 90% of the observations have been less than 1 ppm.

6. Available monitoring data indicate that exposure to VCM around VCM/PVC plants is a local problem confined to within about an 8 km radius. Data in the vicinity of PVC product fabricating plants and other sources are not available.

7. Interim methodology is available for monitoring VCM in the atmosphere, but a standard monitoring system has not been developed.

8. Air inhalation is the primary route of human exposure to VCM.

9. VCM is a primary pollutant, but is atmospherically active and hence a precursor for other pollutants. Little is known about transformation, transport and removal processes. The half-life in sunlight is about 6 hours.

10. VCM in drinking water or food presently does not appear to be a problem.

11. There are no known natural sources of VCM.

12. The emissions data identifying specific point sources in PVC and VCM plants is based on calculations and estimates and is not sufficiently accurate to serve as the basis for the formulation of a quantitative emissions control strategy.

13. The practicality and effectiveness of carbon sorption systems, surveillance-maintenance programs, and deep stripping of the polymer

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remain to be demonstrated as commercially visible control techniques.

14. There are no known studies of damage to vegetation in areas surrounding VCM/PVC plants.

2. INTRODUCTION

Historically, national and international commerce has established markets for new products rarely with due consideration being given to the environmental consequences of the manufacture, use, and disposal of the new products. Consequently, air, water, soil and biota have been contaminated with a wide variety of natural and synthetic chemical compounds that may threaten public health and welfare. The contributory role of a number of chemicals in the production of cancer and other chronic degenerative disease is well known. In the absence of appropriate pre-market testing, assessment of environmental health hazards for many chemical compounds often depends upon retrospective analyses after these products have attained broad multi-media distribution. Establishing prudent standards of environmental quality depends upon the availability of a broad integrated data base that is sufficiently quantitative to permit appropriate risk and benefit assessments to be made.

Until recently, the principal environmental concerns associated with the plastic industry has been waste-water effluents from industrial facilities and the solid waste problems associated with accumulation and disposal of various plastic materials.

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In 1971 the release of phthalate plasticizers from flexible plastic material not only aroused public health concern but served to elucidate a mechanism of transporting potentially hazardous material in a wide-spread fashion. More recent attention has focused upon serious occupational health hazards associated with exposure to vinyl chloride. The basis for this concern is evidence of vinyl chloride carcinogenicity in experimental animals and man.

The predominate commercial importance of vinyl chloride lies in the manufacture of polyvinyl chloride resins which are subsequently manufactured into a large number of useful plastic products. Vinyl chloride may be disseminated on a broad scale as an unreacted monomer entrapped in finished products such as polyvinyl polymers and co-polymers similar to that of the phthalate plasticizers. During the past thirty years, vinyl chloride production has increased from less than 45 million kg in 1943 to more than 2.4 billion kg in 1973. Estimated loss from industrial facilities (both monomer and polymer production) have been placed at over 90 million kg in 1973.

The primary purpose of this report is to provide an interpretive and where possible, quantitative summary of available biomedical effects of vinyl chloride. In this regard, attention is given to gaps in the existing data base.

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Emphasis has been placed upon recent health effects developments, efforts have been made to review and place into perspective the older literature as well.

v. SOME BIOLOGICAL AND STATISTICAL CONSIDERATIONSIN THE ASSESSMENT OF RISKDO NOT DRAFT
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Applying the results of toxicological investigations conducted in the laboratory to the population of interest generally involves two kinds of extrapolations. The first, which is more difficult to deal with and more important with respect to human exposure, involves predicting the probable effects on one species from the results of experiments performed on another. The second kind of extrapolation is that of extending dose-response curves beyond the limited range of observation to determine the dose corresponding to an extremely low incidence of adverse effects on the organism tested.

A. THE ROLE OF THE TOXICOLOGIST IN THE ASSESSMENT OF RISK

This report concerns itself primarily with the task of developing objective technical information needed to make decisions on the course of action to be followed to insure the safe use of chemicals. It does not, except for a general statement of principles, go into the socio-political aspects of decision-making.

Terms such as "toxicological insignificance," "safe," "zero tolerance," "no effect level," and negligible risk" have been in rather common use. All of these contain in one way or another value judgments or technical implications which have no place in an objective assessment of risk. There is no substance which, under certain circumstances, cannot be dangerous and unsafe. There is no battery of tests, however elaborate, which can prove beyond challenge the complete safety of a chemical. For the toxicologist to apply the terms "toxicologically insignificant" or "negligible risk" to a set of observations makes a premature judgment in the wrong arena by the wrong person as to insignificance or acceptability. An attempt has been made to eliminate such terms from this report.

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Another common term of wide usage is the "no effect level." This is statistically meaningless and therefore of limited value since it merely means that no effect was observed in studies using a group of animals of particular size. Such an observation is completely compatible with the presence of an adverse effect, which in further studies with larger sample sizes or with different types of observation might lead to a positive outcome. We prefer the usage of the term "no observed effect," which should always carry with it a qualifying statement as to size of the group in which no adverse effect was observed.

In most instances it will be imperative to develop a dose-response relationship, and because many toxicological techniques are relatively insensitive, high doses (which produce high incidence of effects) are frequently required. These can be and have been called "unrealistic" or "inappropriate." Such exposures may be well above, sometimes many orders of magnitude above, likely levels of exposures to human or wildlife systems. Nevertheless, they are often an essential part of practicable laboratory studies which necessarily use limited numbers of animals. The underlying challenge to the toxicologist is to use these points on the dose-response curve as a means of quantifying responses, and to devise, with suitable margins of safety, appropriate means for extrapolating to realistic, actual exposure conditions. The biological aspects of this extrapolation will be discussed first, and the statistical considerations will be developed later.

B. BIOLOGICAL CONSIDERATIONS

For clarity in the following, it will be assumed that we are concerned with extrapolation from the laboratory situation to human populations.

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Except in the case of lifesaving drugs, only very low risks will normally be accepted in chemical usage. The acceptable risk will, however, vary with the benefit anticipated. In the case of risk of death from a chemical of trivial utility, the acceptable risk would be essentially zero. Put in explicit terms, this might mean 1 death in 100 million persons. As noted in the section on statistics below, extrapolation to such risk levels from experiments on small numbers of animals is extremely uncertain. Again, and as noted repeatedly in this report, the gravity of the effect is a major determinant in an overall assessment of risk. At one extreme lies a fatal outcome, and at the other, a temporary functional alteration producing no disability or discomfort and lying fully within the range of physiological compensation. The susceptibility of human populations varies widely since genetic background, age, prior or co-existent disease are all important determinants, and part of the toxicologist's task is to identify susceptible groups in the population as the basis for establishing limits of exposure.

Another and vital factor constantly facing the toxicologist is the often striking biological differences between the effects of chemicals on laboratory species and on man. It has been repeatedly shown that no one species (including non-human primates) has responses parallel to the human over a wide range of the effects of chemicals. The choice of species must then be based on a determination of the biological similarity in the responses to the chemical under study.

In extrapolating from animals to man the transfer is often made on a dose per unit weight (milligram per kilogram) basis. This practice overlooks the well demonstrated (Freireich et al., 1966) observation that dose per unit surface area (mg/m^2) is generally a better transfer parameter.

There has been much loose talk about "thresholds." The term threshold means "the entrance or beginning point of something." This implies (and is normally so used) a discontinuity in the slope of the dose-response curve. True discontinuities in biological phenomena are rare. However, they do occur. One example is the threshold for glucose excretion by the kidney. Most biological dose-response relationships appear to be smooth functions and in absence of concrete evidence dose-response curves should probably be assumed to be smooth. Many dose-response curves have an "S" shape with a much lower slope at the low end of the curve than in the mid-range. This could be regarded as a "quasi" threshold. The steepness of the dose-response curve is an important consideration for predictive purposes. A steep dose-response curve implies a sharp cutoff (again, a "quasi" threshold) with decreasing dosage.

Some dose-response curves appear to be linear, especially when attention is limited to relatively low incidence rates. One example of this is cigarette smoking and lung cancer (Doll, 1967); there are many experimental situations where this appears to be the case.

Despite the above comments, there are some biological reasons for anticipating that with some chemical agents there may be something approximating a true threshold. The biological basis for this is twofold: (1) the possibility of a relatively greater effectiveness of repair mechanisms at low dose levels; and (2) the possible presence of competing biochemical processes which could convert the chemical to harmless products at low dose levels. It is difficult to generalize on these mechanisms since they can be expected to depend on the chemical and the species. Unfortunately, investigation of these questions has rarely been undertaken.

In the past, these complex considerations have been dealt with programmatically by the use of arbitrary "safety factors."

C. STATISTICAL CONSIDERATIONS

The need for a proper consideration of statistics in the design of toxicological experiments and in the interpretation of the results cannot be overemphasized. First, before meaningful results can be obtained, attention must be given to identifying and reckoning with possible sources of error. Second, statistical techniques are available which can give meaningful estimates of the level of exposure to chemicals corresponding to the level of risk which the decision-maker considers acceptable.

1. Experimental Error and Sampling Error

The outcome of an experiment is normally dependent upon innumerable factors, only some of which are known and even fewer of which are controllable. In dose-response experiments with animals, for example, some identifiable factors influencing the outcome include (1) the composition of the particular batch of test preparation, which typically represents a significant source of variation in independent repetitions of the experiment, (2) animal variability, (3) technician reliability, and (4) the precision of laboratory techniques such as dilution techniques or dose preparation. Since such factors influence the dose-response relationship, they represent sources of experimental error, and hence independent replications which randomly sample the levels of these factors are necessary in order

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estimate their contributions in the measure of experimental error. If major sources of variations are not considered in such replication, then statistical precision as reflected in the width of confidence intervals, for example, may be grossly misleading.

When several major sources of experimental error can be identified, a conceptually simple experimental design would consist of independent replications at each target dose level randomly sampled with respect to all sources of variation. If batches from the chemical manufacturer represent a source of variation, for example, then this design might assign each animal at each dose level to a different batch of chemical from the manufacturer. If dilution errors are non-negligible, then dilutions to target dose should be independent, not only among dose levels but also among animals within dose levels. When such sources of errors exist, this conceptually simple, completely randomized experimental design clearly becomes impracticable, and blocking becomes a more feasible means of conducting the experiment. Thus, each batch of the chemical from the manufacturer might be administered to a group of animals at every test dose to produce, in effect, a separate dose-response curve for each batch. For any one batch, the proportion of animals responding at a given test dose is subject to sampling error due to such factors as animal differences and possible errors in dilution which would result in each animal receiving a slightly different test dose. At any given dose level, the proportion responding also varies among batches; thus, the average proportion responding at a dose level is subject to both sources of error, namely, the sampling error within batches and the variability among batches, which together comprise experimental error. A valid statistical analysis should utilize the appropriate experimental error and not merely its sampling error component.

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Since standard statistical methods of bioassay often are addressed only to the analysis of sampling error, there is need for caution in applying these methods.

2. Estimating Low Effect Levels

Estimation of low effect levels poses a difficult problem. Direct experimental estimation of the level affecting one percent of the population may require several hundred animals to obtain adequate statistical precision. For many reasons, particularly in human populations, much lower risks than one percent are desired. A true no-effect level cannot be observed experimentally. Any observed level has meaning only for a particular sample size.

The observation of no-effect for a group of animals may arise from one of two reasons: (1) the dosage level may indeed be below the theoretical no-effect level; or (2) the number of animals tested may have been inadequate to give a high enough probability of detecting a biologically important change. For example, a test on 20 animals may show no deleterious effect, but a test on 100 animals, tested under the same conditions, may show one or more animals exhibiting deleterious effects. Similarly, for a graded response, a small sample may fail to provide enough statistical precision to detect a change from baseline, whereas a larger sample may. Thus, an observed "no effect level" has no absolute meaning since it depends on sample size and poorly estimates the theoretical "no-effect level"; a better term would be the "no observed effect level."

However, data from experiments in which no effects are observed are useful in placing limits on the probable incidence of effects. For example, if no animals out of 100 animals displayed a deleterious effect, it can be stated with 99% confidence that fewer than 4.5% of animals tested under these conditions

would exhibit deleterious effects. If this level of risk is too high, more animals can be tested. For example, observance of zero animals affected out of 1000 tested results in an upper 99% confidence limit of only 0.46%. To reach an extremely low acceptable risk level in this manner generally requires a prohibitively large number of animals.

The past practice of selecting some arbitrary fraction of "no effect level" as a limit for exposure leaves one with no estimate of risk. However, a fairly conservative estimate of the risk can be made by employing the one-hit (one-particle) theory (Food and Drug Administration Advisory Committee on Protocols for Safety Evaluation, 1971). This theory states that for low dosages, if an experimental dosage is divided by a factor f , then its upper confidence level of the risk is also divided by the factor f . Such an approach will often result in near-zero dosages for extremely small acceptable risks. For example, if zero deleterious responses were observed in 450 animals at a dose d , it can be stated with 99% confidence that the true response rate is less than 1% (one out of 100). The predicted dose for risk of one out of 1,000,000 would then be $10^{-4}d$.

An alternate means of estimating low risk exposure levels involves extrapolation from parametric dose-response curves. Many different empirical mathematical models may be fitted to a set of experimental data (Finney, 1964). The probit and logistic curves have been commonly used in biology, for example, and both curves may fit equally well in the region of experimental observations (2% to 98% response range) but give widely different estimates for extrapolated responses. For example, the probit curve will predict a dosage level approximately 140 times higher than the logistic curve for extrapolation to a dosage expected to elicit one response in 1,000,000 animals. In some instances

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(Doll, 1967) linear dose-response curves have been reported; often, however, these cover only a relatively limited response range.

There is no assurance that the dose-response curve observed in the experimental range of dosages will apply at extremely low response levels. Mantel and Bryan (1961) suggest the use of a presumably conservative slope of one probit for each factor of 10 in dosage level for extrapolating to low levels of carcinogenic risk.

A more recent approach to the extrapolation of laboratory findings to the establishment of standards or limits for human populations (Albert and Altshuler, 1973) has taken into account age at the time of the appearance of the adverse effects as well as the frequency of its occurrence. In the case of cancer from external sources, for example, it has been shown, both experimentally and in humans, that with lower doses cancer appears later, that is, at increasing ages. Under this concept, and assuming the availability of reliable data, it should be possible to establish limits which would place the earliest occurrence of malignancy at an advanced age, e.g., no more than 10% incremental likelihood of cancer at age 95.

D. SUMMARY

In the past, toxicologists have not only made the laboratory assessments of toxicity, but in many instances they have made the final judgment as to the social course to be taken on the basis of a particular set of findings. Instead, the technical experts should be charged with securing an objective independent determination of the extent, nature, and frequency of adverse effects. They should be asked to explain the relative gravity of these effects for the target

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system, be it humans or wildlife. Similarly, other qualified technical experts should be requested to make an objective assessment of the benefits of use and of alternative materials or processes. However, the final judgment as to a trade-off between an adverse health effect and a desired benefit is a social decision and should be made with the participation of those who are affected. This is not to say that technical experts using their technical expertise will not participate, but it does state that they should not be the sole judges of determining the balance between the benefit and the risk.

The dose-response curve is a valuable tool for assessing the safety of a chemical compound. Estimates of low effect levels are part of the information leading to the ultimate designation of safe and acceptable levels. The statistical problems of extrapolation from experimental dose levels to very low levels and the estimation of appropriate errors are particularly troublesome but can be handled if care is taken in the design and analysis of the experiments and the interpretation of results.

Without supporting experimental evidence, however, statistical analysis will never be capable of making the critical extrapolation from laboratory animals to man.

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