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United States
Environmental Protection
Agency

Office of
Noise Abatement and Control
Washington, D.C. 20460

EPA 550/9-81-104
December 1981

Noise

EPA

DETAILED RESEARCH PLAN: CARDIOVASCULAR EFFECTS OF NOISE

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16. ABSTRACT

The effects of long-term (acoustical) noise exposure on the cardiovascular system are the best-documented of the nonauditory physiological effects of noise and represent the greatest potential public health issue. As part of its modest research effort in the noise effects area, EPA has developed the plan contained in this report to organize research in this area, which has been identified by numerous experts as the number one noise effects research priority. This plan includes (1) a summary of what is known from short-term and long-term studies; (2) detailed multicomponent plans for animal experimental studies, human epidemiologic studies, and human experimental studies (3) discussion of recent research, including EPA-sponsored research at University of Miami and Johns Hopkins University, and (4) analysis of five options. It is estimated that if research proceeds according to this plan, decision points will occur in year 3, year 6 and year 8. On the other hand, a "rush program" could be created by simultaneously implementing Options 1-3. Estimates of yearly funding requirements for various options are provided.

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a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
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OF NOISE

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FOREWORD

From 1971 to the present, the Environmental Protection Agency (EPA) has been active in the effort to protect people from excessive noise that may jeopardize their health and welfare. Under the requirements of the Noise Control Act of 1972, as amended by the Quiet Communities Act of 1978, EPA has sponsored a modest research effort on the effects of noise on health, for the ultimate purpose of developing dose-response criteria. The overall goals of the EPA research program have been to improve the noise-related health and welfare data base, refine existing criteria, and develop quantified dose response criteria where they are lacking. These criteria have been needed to support all aspects of environmental noise control programmatic activities, including Federal regulations and technical assistance to state and local governments.

During the past decade a number of national and international scientific bodies and advisory groups have identified the nonauditory physiologic effects of noise as the number one research priority in the noise effects area. More specifically, these recommendations have indicated that primary emphasis should be placed on determining the extent and magnitude of the relationship between long-term noise exposure and cardiovascular system effects. The cardiovascular effects are the best documented of the nonauditory effects, and they represent the greatest potential public health issue.

Based on its legislative mandate and the preceding scientific recommendations, EPA has taken the major responsibility for planning and organizing a program of research in this area. The research plan presented herein constitutes an important aspect of this activity. This plan represents a multifaceted multi-disciplinary program of research on the cardiovascular effects of noise directed at criteria development. EPA, with some assistance from other Federal agencies, has begun to execute selected elements within the initial phases of the plan. Several important studies have been initiated, and some results are available now, with additional results expected by the end of fiscal year 1982.

A basic realignment in national policy has occurred, resulting in an increased role for state and local noise activities and a decreased role for Federal noise programs. As part of this change, the sponsorship of noise effects research by EPA will be phased out by the end of fiscal year 1982. Consequently, EPA is now in the process of completing its ongoing studies and has updated its previous research plans.

The updated research plan as presented here contains a current summary of the state of knowledge with respect to the cardiovascular effects of noise, a detailed presentation of needed research in terms of a series of major initiatives and their respective components, and a discussion of major decision points and research options involved in executing the proposed research program.

It is EPA's intention that this plan and the initial results of studies conducted within the plan serve as a stimulus for other Federal agencies, and the states and research organizations to continue research into this very important area. In effect, the "blueprint" is in place, the end point has been identified, and a number of paths to the goal have been laid out.

1. INTRODUCTION

1.1 Noise as a Health Problem

It is widely accepted that noise is capable of producing a number of adverse consequences on human health and well-being. The most clearly observable and measurable effect of noise is hearing loss, but noise has also been shown to disrupt sleep, interfere with communication, impair task and work performance, adversely affect social and psychological well-being, and to be a source of generalized annoyance.

During the past three decades there has been an increasing concern with the non-auditory physiologic effects of noise. The biologic plausibility of noise acting as a non-specific physiologic stressor is well established, and there is increasing scientific evidence from both the laboratory and the field indicating that noise is capable of producing a number of adverse physiologic responses and health outcomes.

1.1.1 Scientific Recommendations for Research

The scientific community world-wide has recommended that more attention be given to nonauditory physiologic effects of noise. The Third International Congress on Noise as a Public Health Problem (Freiburg, West Germany, 1978), upon reviewing the world literature, emphasized the necessity for giving priority to this area of research. Since the previous International Congress in 1973, at least 123 reports of related research studies have been published in the international literature. These investigative efforts have focused not only on the heart and circulatory system, but also upon effects on vision, fetal development, the digestive system, the muscular system, the nervous system, and the biochemical constituents of such bodily systems.

A recent Workshop of cardiovascular experts at the Massachusetts Institute of Technology underscored the plausibility of the linkage between noise and cardiovascular problems, and urged that a high priority be placed on research in this area, including epidemiological research.

Moreover, a committee (Working Group 81 of the Committee on Hearing, Bioacoustics and Biomechanics) of the National Academy of Sciences has recently recommended that investigation of the relationship between noise and medically significant physiological responses be accelerated, with cardiovascular measures as the initial focus.

The recent World Health Organization criteria report on noise has also emphasized the need for health effects research and pointed out that current national and international research efforts are inadequate given the potential importance and seriousness of the nonauditory health effects of noise.

Finally, the report of an American Heart Association task group convened to examine the impact of the environment on cardiovascular disease has recently recommended that further study be made of the circumstances under which noise produces increases in blood pressure and to define susceptible population groups. It was also recommended that attention be given to the potential relationship between noise and the development of chronic established hypertension and cardiovascular disease.

1.1.2 Severity of the Health Problem

The potential health problem posed by nonauditory physiologic effects is very great. Noise, like other physical stressors, is capable of producing a variety of physiologic stress responses in the body. Stress has been linked to a number of chronic diseases prevalent in our society. Although there are scattered findings associating noise with a number of health problems, the best-documented relationship is the one between noise and elevated blood pressure and related cardiovascular problems. Heart disease ranks as the number one cause of death in America. Hypertension--the most likely specific effect of noise--is a demonstrated risk factor in the development of heart disorders, stroke and kidney disease. It is conservatively estimated that from 23 to 27 million Americans suffer from hypertension. For a very large proportion of these cases (90 percent), the causes are not known; yet hypertension contributes to 250,000 deaths annually in the United States. If, as some evidence suggests, there is a cause-effect relationship between noise and hypertension, the health implications of such a relationship would be considerable. In addition to cardiovascular effects, other nonauditory physiologic effects of noise may be equally serious. That is why it is urgent to find out as soon as possible the extent to which such relationships exist.

1.1.3 Scientific Feasibility

There are some definite conceptual and methodological complexities involved in conducting research on the nonauditory physiologic effects of noise.

Understanding the ways in which noise can change the body's dynamic physiologic systems requires a serious and in-depth program of research. A coordinated program of animal, human clinical, and epidemiological research is essential. Conducting valid research in this area requires the blending of advanced acoustic measurement with sophisticated and detailed monitoring of physiological indicators in both acute and chronic situations. For the most part, the techniques are currently available; the problem is bringing them to bear on the study of noise effects. Much in the way of applicable techniques and procedures are available in research areas such as stress physiology and research on hypertension and cardiovascular disease. The development of quantifiable dose-response criteria depends on the careful and logical accumulation of causal data. It is optimistic to think that any single study or set of studies will yield the type of data needed to establish such causal relationships. Although the problems standing in the way of good research in this category appear formidable, the challenge is not different from that faced in most areas of biomedical research.

1.1.4 Noise Control Program Needs

The need for improved information on the nonauditory physiological effects of noise is very great because noise abatement program activities on Federal, State and local governmental levels are generally based on the need to protect public health and welfare. To the extent that noise effects criteria presently in use (annoyance, hearing loss, activity interference) do not take into consideration some of the most serious effects such as the potential for cardiovascular disorders, they are deficient. The research program presented herein should verify the extent to which a noise/physiologic health relationship exists, and therefore, possibly change both the direction and importance of Federal, State, and local noise abatement activities. Given the current state of knowledge and the projected funding levels, it is unlikely that the first five years of this research program will yield the type of refined, quantified criteria which noise abatement programs will ultimately require. However, depending upon the consistency and magnitude of the findings obtained in the proposed research, it may be possible to propose interim criteria within approximately five years.

1.2 Cardiovascular Effects Focus

The focal point of the research emphasis in the nonauditory effects area is research on noise-related cardiovascular effects, particularly hypertension. Although it is recognized that little is known about any of the possible nonauditory physiological effects of noise, and that the health consequences are potentially great for all of these effects, typical programmatic resource constraints prevent in-depth consideration of all areas simultaneously. If any significant progress is to be made in this area in the relatively near future, a single category of effects must be targeted for intensive, systematic investigation. At the present time, the cardiovascular effects category is the best candidate. This decision is supported by the following points:

- The cardiovascular effects are the best documented of the nonauditory physiologic effects of noise.
- The feasibility of investigating these effects has been demonstrated, and sophisticated techniques are available for application to this area.
- This category of noise effects is potentially linked to a very serious and widespread health problem in the United States.

1.3 Goal of the Cardiovascular Effects Plan

The purpose of this plan is to outline a program of research for studying the cardiovascular effects of noise. <u>The ultimate goal for research on the cardiovascular effects of noise is the development of quantitative dose-response criteria for medically significant physiologic responses such as elevated blood pressure, and for adverse health problems and outcomes related to the cardiovascular system.</u>

Adequate health effects information necessarily serves as the basis for any type of noise control activity. Quantitative dose-response criteria are essential for any type of informed decision-making with respect to choosing among noise control alternatives. At present, there are embarassing gaps in what is known about the effects of noise on humans. In many important effects areas such as the nonauditory physiologic effects, the data base is not adequate to permit the derivation of even tentative criteria. Unfortunately, the areas in which criteria are not available may represent the most serious effects from a public health perspective.

The research initiatives in support of the above goal have been selected and developed with primary consideration given to scientific validity. Major consideration has also been given to the complementary nature of the initiatives and to time and cost factors.

1.4 Criteria Development

The ease with which criteria can be developed in any given area is dependent upon several factors. First, consideration must be given to the current state of science in the area in question. In the cardiovascular effects of noise area, a relatively small empirical foundation exists. However, the blending of acoustic and biomedical research methodology appears to be feasible, and this feasibility has been demonstrated. Directions along which research should proceed have been identified and mapped out. Furthermore, the very large past and present research effort in the areas of hypertension and cardiovascular diseases should provide much in the way of guidance for investigation of noise-related changes.

Second, the ease or difficulty of criteria development is inherently related to the nature of the research area. Some areas are less complex and less multi-factorial than are others. In the case of the cardiovascular effects or other physiologic stress-mediated effects of noise, the level of complexity is great and the number of intervening and individual difference variables to be identified and accounted for is considerable.

Third, the time and effort that will be required to develop dose-response criteria depends upon the adequacy of the research approaches selected. The research plan should form a net that encapsulates the important aspects of the problem through a logical series of interrelated studies. Answers must be pursued in a coordinated fashion and investigative strategies must be appropriate to the problem area.

And fourth, the rate of progress towards criteria is dependent upon the nature of the research outcomes. Although predictions can be advanced and translated into hypotheses and these hypotheses grouped and categorized, a considerable amount of uncertainty surrounds any research program. If there was little uncertainty, there would be little need for research. The rate or progress must be periodically evaluated, so that corrective actions can be taken.

At the present time, it is simply not possible to make definite predictions as to the exact time and effort required to develop criteria in this area. The following program represents the best estimates available at this time. The cardiovascular effects of noise area is complex and one in which relatively little systematic research has been done. The proposed plan takes these factors into consideration, and attempts to draw upon not only what is known about noise-related cardiovascular and other effects, but also what is known about the physiological and psychological aspects of hypertension and cardiovascular disease.

2. RATIONALE FOR SELECTION OF RESEARCH INITIATIVES

2.1 What is Known

Scientific interest in understanding the nonauditory, physiological effects of long-term noise exposure has been evident in one form or another for more than 30 years. The accumulated noise effects literature has been, however, the subject of increasing interest and scrutiny during the past ten years.

It has long been known that noise can act as a general, biologic stressor. The observed effects typify a generalized stress reaction as governed by sympathetic activation of the autonomic nervous system. The hormonal changes produced in animals and humans by exposure to intense sound are essentially the same as those elicited by other stressors. Particularly characteristic is the discharge of ACTH, glucocorticoids and catecholamines.

A substantial body of evidence suggests that noise is capable of producing a number of short-term physiological responses in the organism. Research has examined noise-related reactions in the organism as measured by responses in the adrenal glands, kidneys, heart, blood vessels and blood lipids and platelets. These responses have particular relevance to the understanding of how noise may affect the cardiovascular system. The interrelatedness of cardiovascular system response with the adrenal glands, kidneys, and certain blood constituents is scientifically well established. The following section will present some of the conclusions of studies which have examined the relationship of relatively short-term noise exposure to the above and other physiological responses.

2.1.1 Short-Term Studies

A considerable amount of research has shown that exposure to noise, even to relatively low levels, can reliably produce peripheral vasoconstriction, measured as a change in finger pulse amplitude. This effect appears to be proportional to the intensity of sound, and appears not to completely habituate on either a short- or long-term basis. Also, the vasoconstrictive effects often persist after cessation of the stimulus. At present, there is no direct evidence concerning the pathological significance of this response, however, a recent Scandinavian study has shown that noise exposure can produce increases in total peripheral resistance in humans. The pattern of change called a "defensive response" is similar to a pattern seen in animals, which with repeated stimulation leads to chronic elevations in blood pressure.

It has been known for some time that various psycho-social and physical stimuli including noise can bring about increases in blood pressure. It is also known that individuals differ in terms of the extent to which these stimuli will bring about elevations in blood pressure. Although there are numerous examples of noise-related blood pressure changes in the literature, few conclusions can be drawn at this time because sophisticated investigations aimed at identifying the conditions of noise exposure which produce these elevations and the sub-populations most susceptible have not been initiated.

Research has shown that noise can produce significant alterations in catecholamine levels (epinephrine and norepinephrine) in both human and lower animals. There have been both positive and negative results in this literature due to great variations in methodologies, noise levels and duration employed, and to the fact that very large individual differences in these parameters exist. Other studies have reported significant elevations in cortisol, and tentative evidence exist for lutenizing and growth hormones.

Several experiments have examined serum lipid level in platelet aggregation as a function of noise exposure. From these studies, it appears that cholesterol levels are rarely elevated in experiments lasting less than several hours. Exceptions exist, but for experiments in which extremely high levels of noise were employed. A relationship between noise exposure and platelet aggregation has been demonstrated in rats and rabbits. However, there are no human studies available at this time.

Noise has also been shown to produce changes in respiration rate and to cause slower, deeper breathing. Changes have also been observed in salivary and gastric secretions resulting in a slowing of the digestive process. Evidence also exists which suggests that noise affects gastrointestinal motility.

Effects on the musculoskeletal system have also been reported in terms of increased muscle action potential in response to sound of moderate and high intensities. Other evidence of sympathetic activation comes from studies of the electrodermal response. These studies show lowered electrical resistance in conjunction with sound of high intensity or meaningfulness to the individual.

Inspite of the obvious inconsistencies and gaps in the literature, there does appear to be considerable evidence that exposure to noise under a variety of circumstances is associated with a complex array of interrelated physiological and biochemical reactions in the organism.

2.1.2 Long-Term Studies

The majority of the research on the long-term effects of chronic noise exposure has focused on blood pressure elevations. A number of animal studies using rodents have shown that exposure to noise can cause sustained elevations in blood pressure. The generalizability of the results of these studies is severely restricted due to the proclivity for convulsive behavior (audiogenic seizures) among rodents and to the fact that the structure and function of the rodents' auditory system differs considerably from that of humans.

Recent experimental research using a more appropriate animal model, the rhesus monkey, has shown that as little as several months exposure to environmental noise levels can produce significant sustained elevations in blood pressure of 20 to 30 percent. These observed changes in human patients would be reason for medical concern. In this research, blood pressure was monitored for a full month after the noise was terminated, and there was no evidence of a return to baseline pressures. This later finding suggests that recovery, if it occurs, will take some time. This research also found that the cardiovascular changes occurred at exposure levels not high enough to produce any appreciable hearing loss in the subjects. The laboratory approach has definite advantages in terms of control over extraneous variables and detailed specification and measurement of acoustic parameters and physiological responses. Additional laboratory research with appropriate animal models is required before definite conclusions can be advanced.

The largest body of long-term data consists of retrospective, epidemiologic studies of industrial workers. Approximately 40 such studies exist, most of which were conducted in foreign countries. The most common observation mentioned in these studies is impaired regulation of blood pressure which may be manifested as hypotension, hypertension, or blood pressure lability. Hypotension seems to be more usual in young or new workers and to occur over the course of the workday. Hypertension and blood pressure lability appear to be more prevalent in older noise exposed workers and to be characteristic of a long-term trend in blood pressure.

Other signs and symptoms which have been reported as occurring more frequently and/or to a greater extent in noise exposed workers are: loss of cardiac pacing regulation which can be manifested as either tachycardia or bradycardia, various electrocardiographic anomalies, reduced stroke volume and/or cardiac output, accelerated pulse wave velocity, narrowing of retinal arterioles, blood pressure asymmetries and complaints of generalized chest pains and angina. Translation difficulties and the level of detail contained in the reports of many of these studies make it difficult to assess the precise nature and actual medical significance of some of these findings.

As is often the case with retrospective analyses, most of these studies suffer from one or more methodological shortcomings. There appear to be wide variations in quality within this literature. In many cases, workplace noise levels were only vaguely specified, and little consideration was given to other possible noise exposures. It is also difficult to determine whether or not other environmental stressors such as excessive heat, fumes, dust, etc. were eliminated or controlled. Similarly, it is often difficult to assess the extent to which other cardiovascular risk factors such as weight, smoking habits, etc., were taken into consideraton. The data from some of the studies was amenable to only the most rudimentary statistical treatment. In spite of these and other methodological limitations, the large amount of data and its consistency cannot be ignored. Although the results are associative and primarily qualitative, positive findings have been reported in eleven different countries and 18 different industries. Long-term, prospective data that would support a determination of causality are lacking. Still there remains a fairly large amount of data that suggests that cardiovascular morbidity may be greater among people who are exposed to high noise levels in work situations for relatively long periods of time.

In addition to the industrial data discussed, the results of a number of other recent field studies, conducted in both occupational and residential settings, have emphasized the adverse cardiovascular effects of chronic noise exposure. A group of airport community studies in the Netherlands found evidence of an increased prevalence of heart disease and hypertension in noise-exposed populations as compared to low noise-exposed communities. These effects could not be explained by age, sex, smoking habits, height, weight, or socioeconomic status. Two studies relating children's blood pressure to noise levels in schools and neighborhoods have reported significant noise effects on blood pressure. Increases were reported for both aircraft and street traffic noise.

Several field experiments indicate that systematically varying noise exposure can influence physiologic response. These studies differ from laboratory studies in that they were conducted in naturally occurring settings and/or they involve exposure durations considerably longer than those employed in typical laboratory investigations. In a German study, for example, significant differences in blood pressure and catecholamine levels were observed in the same individuals, in the same work environment, on days of high and low noise exposure. This study is important because it involves comparisons of physiological parameters under different noise exposure conditions while keeping other circumstances the same in a real life setting.

This approach overcomes many of the problems associated with retrospective and cross-sectional studies.

Another experiment sponsored by the U.S. Navy has shown that exposure to short bursts of noise at 80 to 90 dB for 30 days can produce elevations in serum cholesterol levels. The obtained 19 percent difference in cholesterol levels between the exposure and pre-exposure conditions is comparable in magnitude to the difference observed in subjects fed either high or low saturated fat diets, and with differences reported between small groups of subjects who exhibited extremes on instruments designed to measure the coronary prone behavior pattern (Type A and Type B behavior).

A NIOSH sponsored study comparing health measures before and after the initiation of a hearing conservation program found reduced rates of medical complaints and disorders subsequent to the introduction of protective measures. Differences were not found in the control groups where protective measures had not yet been introduced.

2.1.3 Summary

Overall, this literature contains many provocative and potentially important findings related to cardiovascular health. However, from a purely scientific point of view, this literature is characterized by huge gaps in information, numerous inconsistencies in findings, and severe methodological shortcomings. These problems and the resultant qualitative nature of conclusions are largely the result of a total absence of systematic research. The promise of and need for such research is apparent.

2.2 What is Not Known

Although it is known that noise acts as a stressor, it is not known with certainty whether prolonged exposure results in cumulative pathology. Whereas the organism is often capable of adapting to noise at the conscious, behavioral level, elevations in blood pressure and other physiologic changes appear not to reflect habituation. What is the overall medical significance of these physiologic effects? Precise cause-effect relationships need to be drawn between noise and medically significant physiologic responses such as blood pressure, and between noise and the so-called stress diseases or diseases of adaptation.

Information is lacking on the mechanisms underlying noise related changes and the extent to which noise operates in a similar fashion to other, better understood stressors.

Quantitative data are virtually nonexistent concerning the role played by the various physical parameters of noise, including level, frequency spectrum, temporal pattern, and duration. The extent to which nonacoustic factors, or the context in which the noise occurs, mediate the stress effects of noise is not known and should also be specified. This is the type of information necessary to develop quantitative criteria in support of noise control activities.

Attention should be given to identifying those segments of the population that might be particularly susceptible to these effects, for example, children and the elderly. Individual differences should be investigated. Information pertaining to the extent to which chronic noise exposures might exacerbate pre-existing health problems such as hypertension is not available.

2.3 Noise Control Program Priorities

The most important need is to verify as soon as possible the extent to which a cause-effect relationship exists between noise and adverse cardiovascular effects on the grounds that the scope of the potential public health problem is broad. Noise is probably the most pervasive pollutant in the occupational and nonoccupational environment. In recognition of the potential health problem, it was requested in the Quiet Communities Act of 1978 that special emphasis be placed on conducting research on the nonauditory physiologic effects of noise.

A program of research on the cardiovascular effects of noise must involve three general steps:

- The determination of whether or not a valid relationship exists between noise exposure and hypertension and/or other adverse cardiovascular effects.
- The determination of the circumstances under which noise-related cardiovascular effects occur and the identification of sub-populations likely to be most susceptible.
- The determination of the underlying physiological and biochemical mechanisms involved in noise-related cardiovascular system responses.

Statistical associations have been demonstrated between noise, hypertension, and other cardiovascular systems effects, but their ultimate significance awaits further, more sophisticated research aimed at establishing causal relationships. A combination of animal, human clinical and epidemiological research is required. Information should be obtained on the role of various acoustic and nonacoustic variables, and on the susceptibility of various subpopulations to noise-related cardiovascular effects. This type of information is required in order to develop quantitative dose-response criteria. Attention should be given to the examination of basic mechanisms, in that, this information is essential to the full determination of the physiologic impacts of noise exposure. Although a fairly extensive and costly program of research is required, the costs of ignorance are potentially much greater.

2.4 List of Research Initiatives Selected

After reviewing the status of cardiovascular effects research, national noise program needs and priorities, and the planned research activities of other Federal agencies, the following Major Research Initiatives have been selected.

I. Animal Experimental Studies on the Relationship Between Noise, Elevated Blood Pressure and Other Cardiovascular Effects.

II. Epidemiologic Studies on the Relationships Between Long-Term Noise Exposure and Adverse Cardiovascular Effects.

III. Human Studies and Clinical Investigations of Cardiovascular and Neuroendocrine Responses to Noise.

The type of research proposed herein is multi-disciplinary in nature, requiring expertise in a number of biomedical and bioacoustical areas. The participation of more than one agency will insure more effective research design, monitoring and review, and will provide research outcomes with programmatic relevance to more than one agency. Biomedical research is very expensive to conduct, and, where feasible, costs should be shared in order to avoid duplication and superficiality. As pointed out previously, the potential costs of ignorance in this area are great. A concerted program of research is required in order to make significant progress during the course of this Plan.

The relative contribution of each initiative to the ultimate goal of the plan will be determined fairly early in the course of the planned research. By the end of the third year of effort, and prior to the expenditure of the major portion of the proposed funds, it should be possible to determine whether a valid relationship exists between noise exposure elevated blood pressure, and other adverse cardiovascular system effects. Preliminary data on the physiological and biochemical correlates associated with noise-induced cardiovascular changes should also be available. This information should permit empirically founded estimates of the potential extent and magnitude of these effects and of the level of effort required to fully investigate them. The graduated nature of the total program will facilitate the availability of this information prior to the commitment to conduct large-scale dose-response oriented experimental and epidemiologic research.

2.5 Overview

The research plan presented herein reflects a multi-faceted approach to studying stress-mediated physiological effects of noise. The development of criteria for the cardiovascular effects of noise is viewed as being a multi-disciplinary research problem requiring contributions from acoustics and several areas of biomedical and behavioral science. The research approaches or initiatives that will be brought to bear on this program include: animal experimental studies, human epidemiologic approaches, and human investigations and clinical studies. It is recognized that each of these approaches has particular advantages and disadvantages. The intent is that the initiatives will unfold to reflect a systematic and sequential dissection of the problem.

Although each initiative represents a different methodological approach, there are common themes. Each initiative begins by attempting to enjoin the most appropriate and refined research techniques. Where development work is needed to reach this level, the attempt is made to conduct this work prior to the investment of large sums for research. Once techniques are available, research oriented toward criteria development can proceed at an optimum rate. Also, each initiative attempts to produce findings, which, in whatever way appropriate, take into consideration the acoustic, nonacoustic, and predisposing factors known to play a role in determining the effects of environmental stressors such as noise.

2.6 Timing and Funding of Initiatives

In the chapter which follows, each of the planned initiatives is divided into a series of sequential components, and each of these components is described in detail. At the end of the presentation of each initiative, a table is included which contains a summary of the time and funding level required to complete the total initiative and each of the components within the initiative. Although the level of funds available does influence the length of time it will take to complete a given component, the time periods specified were derived primarily with respect to scientific considerations. The objective of this plan is to present a "blueprint" for a coordinated, multi-faceted program of research. The studies are designed to build one upon the other. A certain amount of flexibility with respect to timing and funding is possible, but there are definite limits beyond which a study or component cannot be compressed or stretched as a function of funding level.

The funding levels presented are intended to be representative of the minimum levels required to adequately conduct the research. This plan does not assume unlimited funds. The figures are in 1981 dollars, and there is no provision for inflation.

2.7 Guidance and Monitoring

A Review Panel/Advisory Group should be established to provide guidance and direction to, and periodic review of the total research program. At present, EPA coordinates an interagency health effects research review group which is comprised of representatives of the various Federal Agencies with research-related interests and expertise in noise effects. This group should be supplanted by a group comprised of representatives from both the academic research community and from the relevant Federal Agencies. The membership of this group should not be limited to bioacoustical scientists, but should be representative of the full array of expertise that will be required to conduct this research. As a minimum, the specialties represented should include: cardiovascular and stress physiology, cardiovascular medicine, biostatistics and epidemiology, behavioral science, and physical acoustics. This group should review study protocols and interim and final results, discuss and propose necessary changes to the over-all research plan, and provide a forum for the general discussion of issues and problems in this research area. The group should function, to the extent possible, in a fashion that is independent of established systems for the technical monitoring of grants and contracts for the peer review of proposals.

It is also strongly recommended that the findings obtained in studies that are part of this research program be presented at scientific meetings and published in refereed journals. Furthermore, open scientific symposia and workshops should be scheduled on a regular basis, particularly in advance of the key decision points outlined in Chapter 4. Wherever possible steps should be taken to facilitate objective, scientific evaluation of the results of research conducted as part of this plan. An effort should also be made to ensure that foreign research is taken into consideration and evaluated.

The same steps that are taken to facilitate scientific review and dissemination of findings should also serve to stimulate the scientific community and ensure that a competitive funding environment exist, and that the most qualified investigators and most appropriate research designs are selected for the support.

3. DESCRIPTION OF RESEARCH INITIATIVES

3.1 Initiative I.--Animal Experimental Studies on the Relationship Between Noise, Elevated Blood Pressure and Other Cardiovascular System Effects

Background

The purposes of this initiative are: to assess under controlled conditions the causal relationship between noise exposure and selected medically significant physiological responses, particularly elevations in blood pressure; to investigate the associated pathophysiology; and to begin to develop quantitative dose-response relationships for selected effects using an animal model.

Research with animal models has certain advantages over research with human subjects. In general, the use of animals permits greater experimental control and the use of invasive measurement techniques. These advantages are particularly apparent when long-term or chronic exposure research is required. Animal research with an appropriate model will permit: detailed specification of acoustic parameters, sophisticated and continuous monitoring of physiologic activity, control of extraneous variables, and investigation of underlying mechanisms.

It is particularly important that appropriate animal models be used. The selection of a particular animal for use should not be based on convenience and cost alone. The validity and generalizablility of the research depends upon the selection of an animal with auditory and cardiovascular systems as similar to humans as possible. Although much hypertension research has been done using the rat, the rat appears to be an inappropriate model for noise research because of its tendency towards convulsive behavior and because the auditory structure and function of the rat differ considerably from that of humans. At least for the initial research within this initiative, the non-human primate appears to be the animal of choice for chronic exposure noise research.

It is important to point out that the "megadose type experiment" is not possible with noise because of the possible confounding which would result if the noise stimulus produced appreciable hearing loss during the exposure period. In such cases, reduced sensitivity and/or recruitment would render the results uninterpretable.

At this early stage of research into the relationship between noise and cardiovascular effects, animal studies offer one avenue for overcoming many of the methodological criticisms levied against existing human data. Animal research permits the assessment, under rigidly controlled conditions, of whether noise *per se* causes important changes in parameters of cardiovascular function. Animal research can serve as an effective and cost efficient pre-requisite to more costly and time consuming human research.

Questions exist concerning the generalizability of primate data to the assessment of the cardiovascular effects of noise in humans. This issue will be resolved by comparing the results of the animal studies with those obtained from the epidemiologic and human experimental initiatives. The applicability of the animal data to the eventual development of dose-response criteria will be determined relatively early in the program (see Chapter 4).

Preview

Figure 3-1 portrays the proposed stages of animal research in this area. It is important to note that these stages are not mutually exclusive. For example, a certain amount of information on the physiological and biochemical

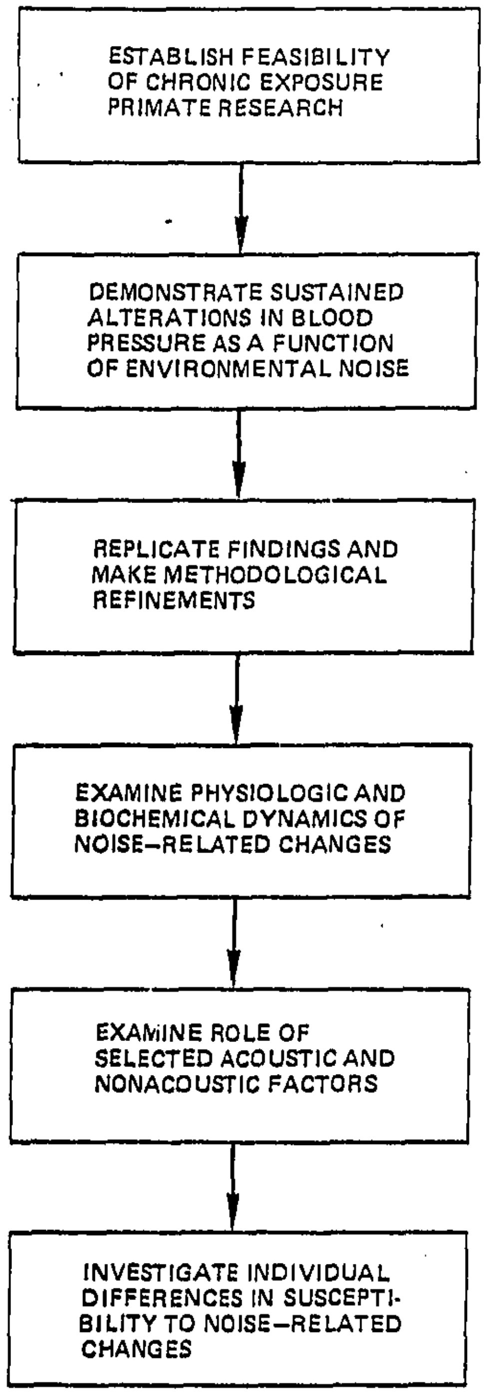

FIGURE 3–1. STAGES OF INQUIRY: ANIMAL EXPERIMENTAL STUDIES

mechanisms involved in noise-related cardiovascular changes is necessary for the design of subsequent experiments. This does not mean, however, that subsequent experiments on the role of acoustic and nonacoustic factors, etc., will generate no new information concerning the physiologic dynamics of these changes. Similarly, research on the contribution of various acoustic and nonacoustic factors need not be distinct from nor necessarily precede research on individual differences.

Research to be accomplished within this initiative can be organized into three general components.

Component I. Preliminary Investigations and Methodological Refinements

The purposes of this component are: to determine the feasibility and applicability of chronic exposure experimentation with primates; to obtain valid experimental data on whether prolonged noise exposure produces sustained alterations in selected parameters of cardiovascular function; to develop the most suitable paradigms for conducting this research; and to obtain preliminary understanding of the physiologic and biochemical mechanisms involved in noise-related cardiovascular effects. The emphasis in these studies should be on collecting detailed long-term data using experimental designs high in internal validity.

Primary emphasis in this initial research should be placed on providing for rigorous experimental control and on obtaining long-term, continuous acoustical and physiological response data. Cost and logistical considerations associated with these requirements will most likely allow that only a few animals be run in any given experiment. It is more important in the early stages of this research to place emphasis toward collecting convincing data on a few animals, as opposed to less convincing and more suspect data on a large number of animals. Experimental designs should be used that permit both between-and within-subject comparisons. In addition to experimental versus control animal comparisons, pre-, per-, and post-exposure comparisons should be done to facilitate assessment of time-related or cumulative effects.

If additional animal research is to be conducted with the objective of eventually deriving dose-response relationships, certain experimental design and procedural refinements should be made as early in the program as possible. This research should be directed at developing the most appropriate, valid, and time- and cost-effective experimental designs for conducting dose-response research. Where possible, investigators should take advantage of "state of the art" techniques and procedures in use in research on hypertension and cardiovascular disease. This research should not only be methodologically oriented, but it should also expand the cardiovascular effects data base.

One procedural question pertains to the durations of noise exposure that are required. Is it necessary to expose the animals for six months or more to noise (as done in the University of Miami study), or would shorter durations be acceptable?

Another procedural question relates to the use of chair restraint. Chair restraint is a widely accepted procedure in primate rsearch. It has the advantages of preventing the animal from removing the physiological recording leads and from making gross movements in space that might make the precise specification of noise exposure difficult. Typically, both experimental and control animals are in restraint, so that obtained differences cannot be attributed to chair restraint *per se*. Chair restraint is not without its critics, however, and it is important that some consideration be given to alternatives to continuous chair restraint. A major benefit of not using long-term, continuous chair restraint is that more animals could be cycled through an experiment in a shorter period of time. There is also research which shows that physiologic responsivity is dampened with chair restraint, suggesting that more pronounced effects might be found using non-restrained animals.

Severe problems in acquiring certain primate species, and the costs and logistics involved in conducting chronic exposure primate research, necessitate that examination be made of the suitability of other species. Important considerations are: the animal's cost and availability, its reactivity to stress, and its previous use and acceptance in cardiovascular and hypertension research. Attention should be given to the possible use of special animal preparations such as animals selectively bred to be predisposed to hypertension. Although the primate is identified here as the animal of choice for use in the initial research within this initiatve, this does not mean that non-primate species would have no utility in any of the planned research.

It is not anticipated that effort within this component will be directed at basic development research; rather, the objective will be to take advantage of techniques previously developed in other related research areas.

Progress To Date

Since 1978, EPA has been sponsoring primate research at the University of Miami Medical School.* Pilot work conducted prior to EPA sponsorship had

*Co-support for the start-up and Phase I portions of the University of Miami study was provided by the National Institute of Environmental Health Sciences of the National Institutes of Health (NIH-NIEHS).

suggested the feasibility of conducting long-term research with primates and had yielded tentative results showing significant elevations in blood pressure as a function of noise exposure.

Phase I of the EPA program, initiated in 1978, utilized four unanesthesized rhesus monkeys (two experimentals/two controls) in restraint chairs, each with an open blood pressure cannulae implanted into the abdominal aorta. After a baseline period of measurement, two of the animals were exposed to a recorded daily 24-hour noise exposure sequence designed to be representative of the occupational and non-occupational exposures experienced by the typical blue collar worker ($L_{eq(24)} = 85$ dB). The animals were exposed to this noise continuously for a period of nine months. The control animals were similarly confined to a low noise environment for the same period of time. After the nine month exposure, measurement was continued on all four animals under the low-noise conditions for an additional month.

The results of Phase I indicated that compared with controls, the net increase in mean blood pressure for the experimental animals was 18.7 mm Hg or 22.9 percent. Blood pressures remained elevated even during the relatively "quiet" portions of the noise exposure sequence. Also, the elevations were sustained in the experimental animals for the full month of post exposure "quiet", demonstrating the apparent persistence of the noise-related effects. Moreover, these cardiovascular effects occurred in the absence of any significant shifts in hearing sensitivity in the noise exposed animals. These findings, published recently in Science, are particularly important in that they suggest that protecting against hearing damage does not necessarily prevent the occurrence of nonauditory effects.

The Phase II replication study initiated in 1980 by the same investigators using the closely related Macaca Fascicularis has also produced sustained elevations in blood-pressure as a function of exposure to the same noise exposure sequence. Stress hormone and blood chemistry data are currently being analyzed.

Phase III, which is presently being initiated, is designed to begin investigation of the cardiovascular dynamics of noise-related changes. This phase will involve the use of circumaortic blood flow probes, epicardial ECG leads and intra-ventricular pressure transducers. These data will be supplemented by complete blood analysis and stress hormone assays and, if warranted, post-mortem examinations.

EPA has also recently begun to sponsor a second program of research using baboons at Johns Hopkins University Medical School. This project will attempt to provide an independent, systematic replication of the University of Miami findings, and will begin to examine the role of selected acoustic parameters and the interaction of noise with other known cardiovascular risk factors.

The preliminary studies recently completed or currently underway do provide some information with respect to some of the methodological issues identified above. It appears from the University of Miami study, that with regard to exposure duration, for example, most of the blood pressure changes occur during the first 30-40 days of exposure. Consequently, future studies need not involve exposures much beyond this duration.

Alternatives to chair restraint are available. Two candidates appear to be the use of tethered animals, and the use of home cage exposure. A tethered animal is still continuously monitored but has a relatively high degree of freedom to move about (relative to chair restraint). Exposing the animal to noise in the home cage will, however, involve removing the animal for the purpose of obtaining physiological response data according to some predetermined schedule. Both of these alternatives involve compromises in terms of precise specification of noise exposure in that the animal does not remain fixed in space with respect to the noise source. Also, in the case of home cage exposures, continuous measurement of physiological response is not feasible. However, various training techniques and sophisticated recording equipment are available that would permit at least frequent, repeated measurement of physiologic response in the animal while it is in the home cage environment. Once the effects have been demonstrated and adequately replicated, then such procedural short-cuts should be attempted since their use would facilitate running more animals and experimental conditions in a shorter period of time. One or both of these alternatives should be tried prior to the initiation of component II.

Component II. Investigations of Acoustic and Nonacoustic Factors

The second component of animal experimental studies should begin to focus on the development of quantitative dose-response criteria using animal models. At this point, valid and reliable data on a relationship between noise exposure, changes in blood pressure, and other related cardiovascular parameters should be available. As useful as this information may be, it provides only a qualitative level of understanding. If substantive effects exist, then the next step is to investigate the role of various acoustic and nonacoustic factors which have been recognized to be of central importance in other noise effects research areas. The purposes of this component will be to assess the relative contribution of these acoustic and nonacoustic factors, and to begin to conduct dose-response oriented animal research.

Detailed work must be done assessing the contribution of various acoustic factors to noise-related cardiovascular responses. Consideration should be given to level, frequency spectrum, temporal pattern, presence of peaks, impulses, etc. Which physical characteristic or characteristics of noise drive the responses? Using methodological refinements developed in Component I, it should be possible to experimentally vary important acoustic parameters.

Research must also examine the extent to which the effects are mediated by various nonacoustic factors. Interest here is with the context in which the noise occurs. Other areas of noise effects research have shown that such contextual factors do contribute in important ways to explaining some of the variance of noise effects. Using well established conditioning and scheduling techniques, it should be possible to manipulate the aversiveness, meaningfulness and controllability of the noise. These are variables which have been shown to be important in other noise effects areas. In such fashion, it should be possible to assess the contribution of these factors in conjunction with various physical noise parameters. For example, noise level and controllability may co-vary in a curvilinear fashion. That is, control over noise may have its greatest influence at moderate noise levels, and less influence at very high and low levels. It is also plausible that the physiological response elicited by a noise associated with adverse consequences may be more severe than that brought about by noise associated with pleasant consequences.

Initial work within this component should seek to determine those acoustic and nonacoustic factors which have the greatest effect on blood pressure and related measures. Once these variables have been identified, more extensive parametric studies should proceed for the purpose of generating dose-response relationships for these factors. Consideration should not be limited to the action of single factors. Thorough examination of the interactive effects is required.

Progress To Date

The findings from the University of Miami study indicate that the blood pressure response appears to be driven by the work place exposure. Subsequent to the replication study, the Johns Hopkins program will begin to systematically vary the acoustic parameters of the industrial noise exposure segment used in the University of Miami study. Attention will be given to level, frequency spectrum and temporal patterning. Consideration will also be given to the role of impulse noise.

Component III. Investigations of Differences in Susceptibility

The purpose of research carried out in this component should be to investigate individual differences in susceptibility to the cardiovascular effects of noise. Previous research, both in noise effects and stress physiology, has shown that the same physical or psycho-social environmental conditions may engender vastly different responses in different individuals. Are there certain factors which predispose or place an organism at greater risk for the cardiovascular effects of noise? Also, how does noise interact with other cardiovascular risk factors? Various risk factor hypotheses suggest that such factors interact in a multiplicative as opposed to additive fashion. It is important not only to understand the contribution of noise but to understand how noise interacts with other known risk factors.

A basic approach to research in this area is to conduct noise studies using some of the specific animal preparations widely used in hypertension and cardiovascular disease research, and to take advantage of experimental paradigms which have been used in stress-related research. Guidance for work in this component comes from what is known about the etiology of hypertension and cardiovascular disease, the risk factors involved in such disorders and the organism's nonspecific response to stress.

Research should proceed using animals selectively bred for hypertension, or animals whose systems have been compromised by various experimental interventions. The intent behind these interventions is to assess the cardiovascular responses to noise of organisms whose systems have been intentionally compromised in an attempt to simulate various human conditions. The list which follows is fairly extensive, and it is recognized that time and budget limitations will restrict the number of factors examined with this research program. One type of intervention would involve behavioral intervention. Research could proceed using animals whose behavioral histories have preconditioned them to be hyper-reactive to stress. One way to accomplish this would be to use animals pretreated in an uncontrollable shock or other related situation. A second category of intervention would involve surgical procedures such as de-afferentation of the carotid sinus and an aortic arch baroreceptor, renal artery stenosis or extensive resectioning of functioning renal mass. A third category would involve the infusion of hormones such as angiotensin II, norepinephrine, or cortisol. A fourth category would include dietary manipulations, for example, the administration of large amounts of sodium. A fifth category would include the use of pharmacological approaches such as the administration of amphetamines or nicotine. A sixth category could also be included which would examine the interaction of noise with various toxic chemicals and/or other contaminants prevalent in environmental settings.

Other animal research shows that very young animals are more sensitive to factors known to influence blood pressure than are older animals. This observation, combined with tentative blood pressure findings in noise-exposed children, suggests the importance of the age variable.

Initial work within this component should be aimed at empirically determining those factors which render the organism susceptible to the cardiovascular effects of noise. Next, in more detailed studies, these factors should be combined with each other, and with selected acoustic and nonacoustic factors in order to determine the extent and magnitude of the interactive effects.

Progress To Date

The Johns Hopkins program will begin to look at the interaction of noise exposure with other factors known to be related to cardiovascular system response and hypertension. Experimentation will investigate the interaction of noise and salt intake. A number of theoretical formulations link the development of hypertension to break-downs in sodium and fluid balance. The combined effects of salt and noise may be greater than would be predicted from the two factors taken separately. Examination will also be made of the interaction of noise with pre-existing blood pressure elevation. Some evidence exists which suggests that "stress" accelerates blood pressure increases more in border-line or hypertensive organisms than in normotensive organisms. These two studies will begin to provide some information concerning the interactive effects of noise and also begin the process of identifying potentially susceptible sub-populations.

Funding

Table 3-1 contains a summary of estimated funding levels for the Animal Experimental Studies Initiative.

Expected Results

The expected results for the Animal Experimental Studies Initiative, broken down by components, are presented below in outline form.

Component I. Preliminary Investigations and Methodologic Refinements

- o Continue Expanded University of Miami Study
  - replications of initial findings
  - investigation of physiological and biochemical mechanisms
- o Initiate Additional Primate Studies
  - independent replications of University of Miami findings
  - methodological refinements/development of conceptual models

Component II. Investigations of Acoustic and Nonacoustic Factors

- o Parametric Studies of Selected Acoustic/Nonacoustic Factors
  - relationship of physical parameters of noise to cardiovascular and other related physiologic responses
  - interaction of acoustic/nonacoustic parameters on cardiovascular and other related physiologic responses

Component III. Investigations of Differences in Susceptibility

- o Systematic Studies Using Animal Preparations Possibly Hypersusceptible to Effects of Noise

TABLE 3-1

FUNDING SUMMARY FOR ANIMAL EXPERIMENTAL STUDIES INITIATIVE
(Thousands of Dollars)

YEAR	1	2	3	4	5	6	7	8	TOTAL
COMPONENT I	300	450	500	--	--	--	--	--	1250
COMPONENT II	--	--	--	400	450	450	450	300	2050
COMPONENT III	--	--	--	250	250	250	250	250	1250
TOTAL	300	450	500	650	700	700	700	550	4550

note: To date, EPA has provided approximately 850 thousand dollars of support for animal experimental research. NIH-NIEHS has provided approximately 110 thousand dollars. Most of these funds have been applied to years one to three of Component I.

- identification of factors which place organism at risk for noise-related cardiovascular effects
- determination of whether noise exacerbates certain pre-existing health conditions

3.2 Initiative II.--Epidemiologic Studies on the Relationship Between Long-Term Exposure and Adverse Cardiovsscular Effects

Background

The purposes of these studies are: to provide valid epidemiologic data on the relationship of long-term noise exposure and adverse cardiovascular effects, particularly hypertension; to determine the extent to which a causal relationship exists between noise and cardiovascular disease; and to obtain data useful in deriving criteria for estimating the effects of noise on hypertension and cardiovascular disease.

Epidemiologic or population-based studies serve as a necessary complement to animal and human experimental research. Epidemiologic studies can best provide information on chronic effects of noise on human health in populations of diverse susceptibility. Noise is rarely the only risk factor present in any specific environment. By quantifying and comparing risks, population-based studies can serve to clarify the significance of varying levels of noise exposure on individuals living in uncontrolled environments, coping with combinations of environmental stimuli simultaneously with noise.

It must be recognized that there are no perfect epidemiologic studies. Epidemiology is done in field settings and the advantages and disadvantages of such naturally occurring situations must be accepted to some degree. The epidemiologist simply cannot exert the control or manipulate variables with the same precision as can the experimentalist. There is a trade-off between ecological validity and research control. The epidemiologist in deriving conclusions relies on replication. The emphasis is on the internal consistency of findings.

A program of epidemiologic research typically follows a series of steps. Initially, concern is with description of the frequency and distribution of disease, with comparisons of its frequency in different populations and in different segments of the same population (descriptive epidemiology). Next, this descriptive data is coupled with clinical or laboratory observations, to formulate hypotheses linking disease frequency to more or less specific population characteristics or exposures. Then, these hypotheses are tested through investigations based on observations of specific groups of individuals (analytic or experimental epidemiology). There are two phases to testing an epidemiologic hypothesis: (1) a demonstration of the association, and (2) a determination of causality.

Analytic epidemiologic studies are generally categorized as being either prospective or retrospective. A prospective study is one in which the progression of inquiry is from a supposed cause to an effect, while a retrospective study is one in which the beginning point is the effect and the inquiry is made regarding antecedent conditions which relate to the effect. One of the major disadvantages of the retrospective approach is that the investigator must attribute current health states to some previous occurrence (e.g., history of noise exposure). The prospective approach generally begins with the assessment of current health status, followed by longitudinal assessment of health changes as a function of some event or occurrence such as noise exposure.

Virtually all previous epidemiologic work on the cardiovascular effects of noise has been retrospective in nature. This is a definite problem in that it is extremely difficult to isolate and specify previous noise exposures or to discount other environmental variables that could have produced the observed effect. Retrospective studies are often conducted preliminary to more definitive prospective studies. Associative data is frequently acquired through retrospective research, while casual data is obtained through longer-term and more difficult prospective research.

Preview

Figure 3-2 portrays the stages of epidemiologic research on the cardiovascular effects of noise. The stages, to some extent, parallel the stages of epidemiologic inquiry discussed above. The sequence of the stages is not invariant. Effort in more than one stage at a time is possible.

The epidemiologic research to be conducted can be organized according to three components.

Component I. Retrospective Analysis

The purposes of this component are: to evaluate the adequacy of existing epidemiological data on the nonauditory physiological effects of noise; to assess the advantages and disadvantages of various epidemiological methodologies; and to obtain, if warranted, additional valid retrospective data.

A number of foreign retrospective studies suggest a relationship between long-term exposure to industrial noise and various adverse cardiovascular system responses and outcomes. However, much of this literature is not available in English and consequently it has not been thoroughly critiqued and evaluated by experts in epidemiology, biostatistics, and cardiovascular medicine. Thus,

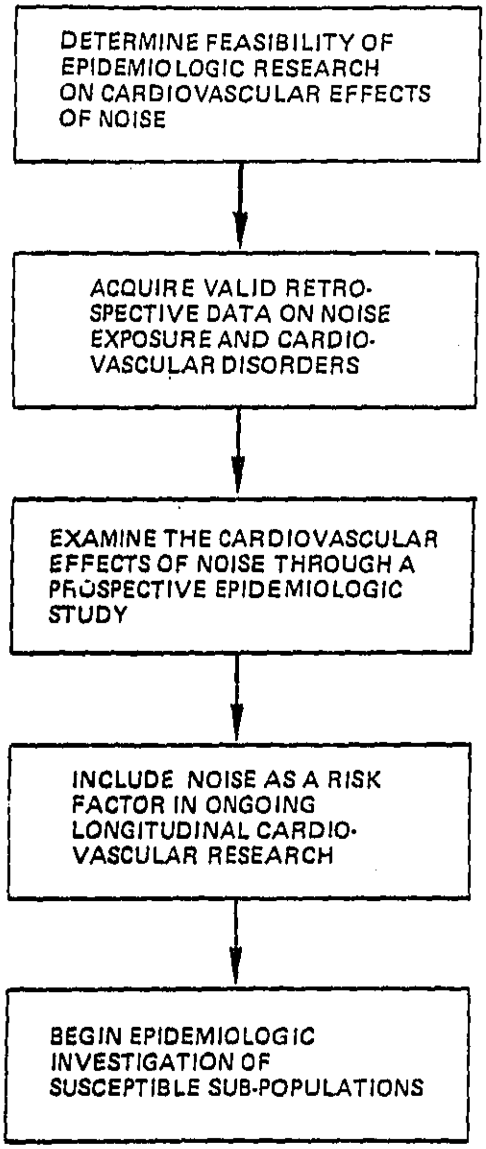

FIGURE 3–2. STAGES OF INQUIRY: EPIDEMIOLOGIC STUDIES

at the present time, it is very difficult to generalize from these data with confidence or to determine the full import of the findings. It is also difficult to determine with precision what is known and not known about these effects, or to determine specific data gaps and research needs. Prior to the initiation of large-scale epidemiologic research on the nonauditory physiologic effects of noise, a thorough and critical analysis of this literature should be conducted.

Progress to Date

In 1980, EPA initiated an epidemiology feasibility study on the cardiovascular effects of noise. This study had three purposes: First, it was intended to provide an objective and detailed analysis and evaluation of existing epidemiologic literature on the nonauditory effects of noise. Second, the study was intended to assess the applicability of non-noise related research on hypertension, cardiovascular disease and stress physiology to the investigation of noise effects. And third, the study was to discuss and make recommendations regarding a number of substantive and methodological issues that must be considered in designing a program of epidemiologic research on the nonauditory health effects of noise.

Preliminary results from the feasibility study indicate that few of the existing studies are adequate with respect to current standards for epidemiologic research, and that there exists a definite need for both valid retrospective and prospective data. The final results of this study should be directly applicable to the design of future epidemiologic studies.

A second study initiated by EPA in 1980 involves analysis of data from the 1971 to 1975 National Health and Nutrition Examination Survey (HANES).

Although the primary purpose of this project is assessment of the prevalence of noise-induced hearing loss in the population, an attempt will be made to examine the relationship between noise exposure, hearing loss, and various health problems such as hypertension, cardiovascular disease, gastrointestinal disorders, etc. Indirect indices of noise exposure will be derived from occupational codes and other related information. Preliminary results of the auditory portion of the analysis appear to suggest the efficacy of this approach.

The HANES project takes advantage of a very large data base which contains extensive health examination and self-report data. The nonauditory effects analysis will focus on modelling associations between noise exposure, background characteristics and health status, and hypertension. Self-report data on the history of a variety of conditions will be evaluated as will the results of the general medical examination. Results of the general well-being questionnaire will be used as indicators of emotional stress. Drug and medication usage data will also be analysed. Selected biochemical indicators will similarily be examined for their possible associations with noise exposure.

An epidemiologic study of the effects of occupational noise exposure on hypertension has recently been initiated by the University of Pittsburgh with support from the National Institute of Health - National Heart, Lung and Blood Institute (NIH-NHLBI). The primary objective of this study will be to determine whether noise exposed individuals have elevations in blood pressure independent of other known risk factors for high blood pressure. The study population will consist of a sample of 250 male hourly workers from a noise exposed group and 250 male hourly workers from a control group. The sample will include employees between 40-60 years old, who have worked at that particular plant for at least 10 consecutive years. The clinical examination will consist of height, weight, pulse and blood pressure, and audiometric evaluation. A questionnaire concerning present and past health status, present smoking habits, and current alcohol consumption will be administered. Data on past military history, previous job exposure, hobbies and medication will be obtained. In addition, a battery of psychological tests will be administered to the participants in order to determine the relationship between noise, behavior, and changes in blood pressure.

Positive results in the Pittsburgh study would serve to validate some of the previous foreign studies. Taken together, the results to be obtained in projects underway in Component I should provide considerable guidance for work to be initiated in successive components.

Component II. Prospective Analysis

Phase I - Small Scale Prospective Study

A relatively small scale prospective study should be initiated, directed at assessing in a valid manner the casual relationship between noise and cardiovascular system effects. The necessity for this type of study and the precise form it will take are dependent on the results of work scheduled to be undertaken in Component I of this initiative. To the extent possible, the results of the initial animal and human experimental studies should also be taken into consideration in developing prospective studies in this area.

A thorough planning and review stage should precede the conduct of any prospective research. Prospective studies are costly and time consuming, and adequate provisions should be made for effective study implementation and management, and to insure that the study will yield interpretable, high quality data.

The trend in stress-related hypertension research is toward small scale, but intensive prospective studies, often involving some form of intervention or manipulation. In other words, the epidemiologic study takes on some of the characteristics of the classical experiment. A variant of this approach has been called process oriented, in that the actual transactional processes taking place between a given type of individual and given environmental conditions are studied. With respect to noise, the approach might be to study variations in blood pressure concurrently with variations in noise exposure. Here, the approach is intra-individual as well as inter-individual, or, as it has been called elsewhere, ipsative-normative research. A preliminary attempt to apply this approach to a noise study has been carried out by a German investigator with some success. In this study, differences in blood pressure and the levels of various stress-related hormones were found in the same individuals on days of high and low noise exposure.

Recommendations made by previous working groups and scientific bodies have suggested that such a small-scale study might best be conducted in a work setting and that the study should involve some type of intervention such as the institution of a hearing conservation program or other type of noise control measure. Work settings represent environments in which a reasonable amount of control is possible, and they might also be viewed as representing "worst case" situations. An attempt should be made to control for all the important variables affecting the outcome measures except noise. Detailed noise measures should be made of the current environment and should be repeated on a regular basis throughout the study. Dosimeters should be used to determine individual noise exposures, both inside and outside the work environment, over 24-hour periods. At a minimum, the project should include unbiased multiple measures of blood pressure, electrocardiograms (perhaps some type of continuous monitoring), assessment of hormonal responses to noise, standard blood chemistry, and hearing acuity. Emphasis should be placed on those individuals at high risk. Detailed medical histories and noise exposure histories should be obtained as well as symptom checklists and demographic, socio-economic, behavioral and physiological indicators. Data collection should span a period of at least two and one-half years.

An important, although costly, element of an intensive examination of the effects of noise on blood pressure regulation would involve continuous measurement of blood pressure during noise and quiet. Portable automatic recording sphygmomanometers and related equipment are available for this purpose. Using such procedures, comparisons <u>between</u> individuals actually in high and low noise environments could be made as well as <u>intra-individual</u> comparisons during intervals or days of high and low noise exposure. Measurements such as these, done repeatedly in a longitudinal study, would provide an extremely rich and valuable source of data. Systolic and diastolic mean blood pressures, ranges, and maximums could be obtained with such a measurement regime.

The prospective nature of the study will permit the assessment of changes in blood pressure over time as a function of prolonged noise exposure. Initial measurements will permit the identification of those who may be categorized as normotensive, borderline, or hypertensive at the beginning of the study. Thus, it will be possible to determine whether blood pressure increases for certain individuals during the course of the study place them into a new category. This information could be combined with data from the continuous monitoring studies to provide explanations of the way in which these "affected" individuals react to noise and also how these reactions changed over the course of the study. This type of information would be invaluable in providing an understanding of how noise influences blood pressure over time, while at the same time, providing a means of identifying noise-sensitive and/or pre-hypertensive individuals - an "early warning signal".

Phase II - Inclusion of Noise as a Factor in Ongoing Longitudinal Cardiovascular Research

The small-scale prospective study (Phase I) will be useful in determining the extent to which a causal relationship exists between noise and hypertension and other cardiovascular disorders. Although the Phase I study will provide an important verification of this relationship, the sample size and variety of noise conditions examined will be by necessity rather limited. Once a causal relationship is indicated, it remains important to determine the actual medical significance of noise exposure and the general shape of the dose-response relationship. The existence of a dose-response relationship is in and of itself strong evidence for causality. If promising results are obtained in Phase I, an attempt should be made to include actual noise exposure as a factor in ongoing and/or planned large-scale NIH longitudinal cardiovascular research. Although detail must be compromised to some extent in this type of study, a large-scale study is the only means of obtaining data on a substantial number of different types of individuals exposed to vastly different noise conditions. It is through this method of study that it will be possible to assess the circumstances under which noise contributes to the hypertensive and cardiovascular disease process. Given a very large sample size, noise exposure information must be obtained through a carefully designed set of questions directed at assessing the past and present occupational and nonoccupational exposures. Some of the shortcomings of this indirect approach may be avoided given that the individuals would be followed prospectively. This inventory should be repeated periodically throughout the course of the study. Actual noise measurements and dosimeters should be employed on selected subsamples of study participants.

Measurements of noise exposure should be combined with measurements of other risk factors such as improper diet, cigarette smoking, hypertension, high levels of serum cholesterol, sedentary lifestyle, and diabetes mellitus. These studies will contribute greatly to knowledge concerning the effects of noise in relation to other risk factors for cardiovascular disease. It is only through such research that the contribution of noise relative to other risk factors can be assessed in a sample large enough to permit generalization. Such an effort would contribute greatly to the development of valid dose-response criteria.

Component III. Investigations of Special Sub-Populations

Phase I - Blood Pressure in Children

Tentative data concerning elevations in blood pressure and a fairly extensive literature on cognitive development suggest that children may constitute a population susceptible to the nonauditory effects of noise. Thus, children are identified herein as the initial sub-population of concern, one requiring early study. The biomedical research community has also expressed concern about the problems of essential hypertension in children and the predictive value of childhood blood pressure lability and elevation. A basic question involves the relative contributions of genetic and environmental factors in the development of blood pressure elevations in children. In the third year of the plan, an initial investigation should be undertaken to examine the role of noise in one of several ways: (1) an expansion of the EPA sponsored Fels Research Institute longitudinal hearing loss study, (2) adding noise exposure measurements to one of the several ongoing childhood blood pressure studies sponsored by NIH, or (3) including blood pressure as a component in planned research on the effects of noise on cognitive and language development and school performance.

Funding

Table 3-2 contains a summary of estimated funding levels, for the Epidemiological Studies Initiative.

Expected Results

The expected results for the Epidemiological Studies Initiative, broken down by components, are presented below in outline form.

Component I. Retrospective Analysis

- o Valid Replication of Existing Epidemiologic Data
    - establishment of association between noise and cardiovascular responses

TABLE 3-2

FUNDING SUMMARY FOR EPIDEMIOLOGICAL INITIATIVE
(Thousands of Dollars)

YEAR	1	2	3	4	5	6	7	8	TOTAL
COMPONENT I	200	250	--	--	--	--	--	--	450
COMPONENT II	--	200	700	750	650	500	500	500	3800
(PHASE 1)		(200)	(700)	(750)	(650)				(2300)
(PHASE 2)						(500)	(500)	(500)	(1500)
COMPONENT III	--	--	250	250	250	--	--	--	750
TOTAL	200	450	950	1000	900	500	500	500	5000

note: To date, EPA has provided approximately 200 thousand dollars of support for epidemiologic research. NIH-NHLBI has provided approximately 150 thousand dollars of support through its sponsorship of the University of Pittsburgh study. All of these funds have been applied to years one and two of Component I.

Component II. Prospective Analysis

- o Small-scale Prospective Study (Phase I)
  - test of causal relationship between noise and cardiovascular responses
- o Inclusion of Noise in Large-scale Longitudinal Research (Phase II)
  - obtain generalizable data regarding cardiovascular effects of noise
  - extract dose-response information on cardiovascular effects of noise

Component III. Investigations of Special Sub-Populations

- o Blood Pressure in Children
  - determine if children are particularly susceptible to cardiovascular effects of noise

3.3 Initiative III.--Human Studies and Clinical Investigations of Cardiovascular and Neuroendocrine Responses to Noise

Background

The purpose of this initiative is to determine the effects of noise on blood pressure, cardiovascular function, metabolic activity, and endocrine response under controlled conditions. Laboratory and field investigations employing experimental and quasi-experimental designs provide an important complement to animal and human epidemiologic research.

Almost all of the previous laboratory studies of human physiological response to noise have focused on short-term or phasic responses to brief presentation of simple acoustic stimuli. It is well-known that such presentations can elicit a number of cardiovascular and other physiological responses. However, many of these same responses, as elements of an orienting reflex, are often subject to rapid habituation. More recently, other studies have suggested that noise is capable of producing relatively longer-term or tonic physiological responses.

In this area of research, there is a definite need to take advantage of the availability of more detailed and sophisticated experimental procedures. For example, multi-session and multi-day experiments need to be conducted. Monitoring of physiologic and biochemical activity must be carried out subsequent to termination of noise stimulation, or on a 24-hour basis. Where possible, advantage should be taken of mobile labs for field research and residential labs for longer-term laboratory studies. Approaches such as these will permit the careful examination of the time course of response, recovery and adaptation. Such studies will also facilitate the collection of new information on the effects of noise on affective state, performance, sleep, and the pattern of interaction between these effects and physiological response.

In particular, the characteristics of noise which produce cardiovascular and neuroendocrine responses should be examined as well as the characteristics of subjects most susceptible to the physiological effects of noise. Explicit attention should be given to situational and contextual variables and to the way in which noise interacts with other environmental and psychosocial stressors. Eventually, it will be possible to identify sources of noise and conditions of exposure to noise most likely to cause cardiovascular disease, and to identify people at greatest risk for developing cardiovascular disease when exposed repeatedly to noise over long periods of time.

Preview

Figure 3-3 contains a portrayal of the stages of human investigations and clinical studies on the cardiovascular effects of noise. Again, as was the case with the animal experimental studies, these stages should not be viewed as being completely mutually exclusive.

Component I. Preliminary Investigations

The primary emphasis of research conducted within this component should be the examination of noise-related physiological responses in humans under controlled conditions. Detailed determination of time-related changes in response, recovery, and adaptation as a function of exposure to selected noise conditions should be made. Dependent measures should include: blood pressure, pulse rate, peripheral vasoconstriction, skin impedance, skin temperature, catecholamines and other biochemical parameters, etc. Important advances in biochemical assay procedures and physiological recording techniques and instrumentation have been made since some of the early noise effects studies were conducted. Studies carried out in this component should take advantage of these developments to the extent possible. The attempt should be made to employ exposures of greater duration than those employed in previous studies, and to use repeated measure designs and sophisticated tests of statistical significance.

Progress to Date

Research recently initiated at the John Hopkins University under EPA sponsorship is directed at assessing the relationship between noise stress and aspects of human cardiovascular functions. The schedule of proposed experiments is designed to study, in a parametric and controlled fashion, the

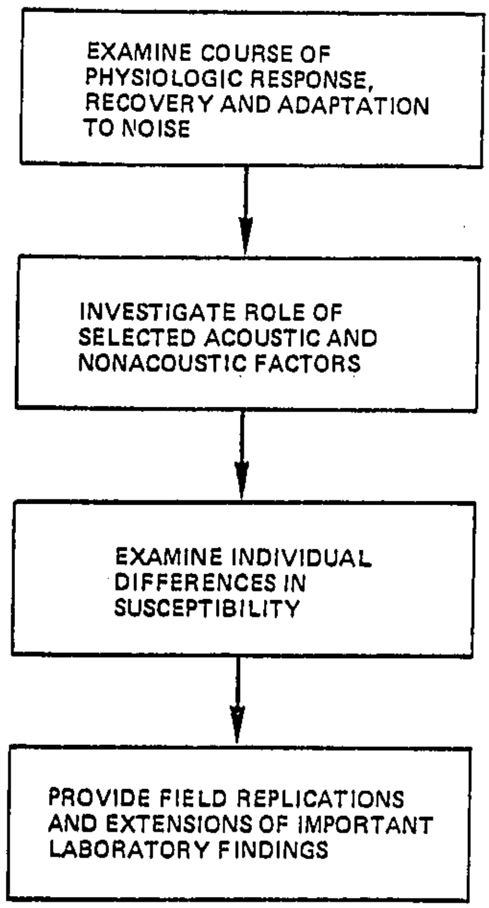

FIGURE 3–3. STAGES OF INQUIRY: HUMAN STUDIES AND CLINICAL INVESTIGATIONS

effects of the basic properties of the noise stimulus, the pattern of physiological response, the pattern of change over time associated with repetitious stimulation by noise, and the interaction of the effects of noise with simulated work stress and resting baseline blood pressure. Three experiments are to be conducted. Experiment I will explore selected acoustical variables and their effect on blood pressure. Three types of noise stimuli (steady-state continuous, random intermittent, and impulse-type) at two different sound levels will be used to elicit the changes in blood pressure level. That combination of noise type and sound level which brings about the greatest acute blood pressure response will be used in experiments II and III. Experiment II will pair noise exposure with simulated work stress at three levels of difficulty: no work, moderate, and high difficulty. That level of work difficulty which produces the greatest change in blood pressure will be used in experiment III. Experiment III will be conducted in a residential laboratory environment. Two groups of subjects, persons with high normal versus low normal blood pressure, will live in the laboratory in groups of four at a time. Physiological function, blood and urinary parameters, and performance will be monitored over a period of nine days. The first two days will permit the establishment of baseline data with no noise exposure; five days of noise exposure will follow; then two days of relative quiet will allow observations of the sequelae of the noise exposure. All subjects will receive audiometric evaluations before, during, and after exposure.

The results of this study should provide initial information pertinent to the purposes of each of the three human studies components, and should provide considerable guidance for the design of future studies, and toward evaluating the promise of the total human studies and clinical investigations initiative.

Component II. Investigations of Acoustic and Nonacoustic Factors

Systematic attention should be given to the role of acoustic factors such as level, frequency spectrum, and temporal pattern. The effects of these factors should be assessed by elevations in blood pressure, blood lipid levels and concentrations of hormones that are associated with cardiovascular and metabolic function of human subjects.

The effects of nonacoustic factors should also be studied systematically. Physiological effects of noise appear to be aggravated by the type of noise, what the noise is associated with, where and when the noise occurs, and possibilities for controlling the noise. Investigations should be carried out to assess the role of contextual factors such as controllability, meaning, familiarity, contingencies, and task load. This research will provide answers to important questions such as the following: (1) What is the relationship between an individual's self-report annoyance reaction to noise and his/her physiological response? (2) Is annoyance a verbalized symptom of physiologic stress? (3) Does noise exact a greater physiologic toll when it disrupts ongoing performance or activity, when its onset is unpredictable or uncontrollable, or when it is unfamiliar or associated with negative consequences? These and other questions have important implications for noise control activities. It is possible that activity interference, annoyance reactions, and performance effects may be secondary reactions to, or symptoms of, noise-elicited physiologic stress.

Work within this component should commence with examination of the influence of selected acoustic parameters on physiologic response, recovery and adaptation. Next, various nonacoustic factors should be introduced so that a determination can be made of how much variance is explained by these factors.

Progress to Date

The recently initiated Johns Hopkins human experimental study will provide some information on the role of selected acoustic factors. Preliminary human response data will be obtained concerning the effects of different noise levels, continuous versus intermittent noise, and on the effects of impulse-type noise. Data will also be gathered on the interaction of noise exposure with varying task performance demands.

Component III. Investigations of Differences in Susceptibility

Experiments will be conducted to determine which individuals are most susceptible to effects of noise on cardiovascular and metabolic function. Not all individuals appear to be equally affected by noise and some may not be affected at all. However, individuals with high levels of blood pressure and individuals with labile blood pressure may be affected more than others, while individuals with neurogenic forms of hypertension may be affected most of all. There is reason to believe that individuals displaying the coronary-prone Type A behavior pattern and individuals who have been chronically exposed to noise may display exaggerated or idiosyncratic physiological responses to noise. Care must be taken in designing these studies to comply with regulations governing the use of human subjects.

Those subjects most susceptible to adverse effects should be identified in controlled laboratory experiments with measurements of physiological responses caused by noise. Those acoustic and nonacoustic factors most likely to aggravate effects of noise should be introduced systematically to determine which individuals are most affected by noise under the most extreme conditions. Dose-response relationships should then be determined with each type of individual in each experimental situation. Eventually, studies of susceptible individuals should be carried out in a long-term field study under exposures to different levels of noise.

Progress to Date

Experiment III of the Johns Hopkins study will involve an attempt to use subjects who have low and high normal resting blood pressure. This study, by introducing the subject variable of blood pressure, represents an initial attempt to investigate in a chronic exposure situation, one factor which the literature suggests may be related to susceptibility to stress effects.

Funding

Table 3-3 contains a summary of estimated funding levels for the Human Investigations and Clinical Studies Initiative.

Expected Results

The expected results for the Human Investigations and Clinical Studies Initiative, broken down by components, are presented below in outline form.

Component I. Preliminary Investigations

- o Investigations of the time course of physiologic response, recovery and adaption
  - demonstration of effects using most appropriate experimental designs, exposure durations and dependent measures

Component II. Investigations of Acoustic and Nonacoustic Factors

- o Parametric Studies of Selected Acoustic/Nonacoustic Factors
  - relationship of physical parameters of noise to cardiovascular and other related physiologic responses

TABLE 3-3

FUNDING SUMMARY FOR HUMAN STUDIES AND CLINICAL INVESTIGATION
(Thousands of Dollars)

YEAR	1	2	3	4	5	6	7	8	TOTAL
COMPONENT I	150	150	--	--	--	--	--	--	300
COMPONENT II	--	200	300	300	300	300	--	--	1400
COMPONENT III	--	200	200	300	300	300	--	--	1300
TOTAL	150	550	500	600	600	600	0	0	3000

note: To date, EPA has provided approximately 150 thousand dollars of support for human experimental research. These funds have been applied to years one and two of Component I.

- interaction of acoustic/nonacoustic parameters and cardiovascular and other related physiologic responses

Component III. Investigations of Differences in Susceptibility

- Systematic Studies of Individuals Potentially Hypersusceptible to Effects of Noise

  - identification of factors which place an organism at risk for noise-related cardiovascular effects

  - determination of whether noise exacerbates certain pre-existing health conditions

3.4 Other Required Research

It is not possible to completely specify all of the research needed to develop criteria for the cardiovascular effects of noise. For example, it is possible that additional human field studies will be required to validate the laboratory findings obtained within Initiative III. It is reasonable to assume that some redirection of effort will occur, resulting in the need to place additional funds into selected initiatives or components.

4. DECISION POINTS AND RESEARCH OPTIONS

4.1 Decision Points

As the flow chart (Figure 4-1) indicates, there are essentially three major decision points in the cardiovascular effects research program. If research proceeds as planned, they will occur in year 3, year 6, and year 8, respectively.

Decision Point 1 (Year 3)

By year 3, the University of Miami Study will be completed and chronic exposure data will have been accumulated on 12 to 16 animals for the purposes of demonstrating whether or not sustained elevations in blood pressure occur as a function of prolonged noise exposure. Preliminary data will also be available on the biochemical and physiological processes underlying these changes. Other animal research should have provided independent replication and extension of the University of Miami findings, and some preliminary information should be available on the role of selected acoustic and nonacoustic factors. Substantial progress should have been made towards developing a streamlined procedure for conducting cost and time-effective dose-response research using primates.

Following the plan presented in this report, a retrospective epidemiologic study will have been completed, providing a test of the existence of a statistical association between long-term noise exposure and elevated blood pressure. The HANES data analysis project will also have been completed, providing some additional data on the relationship between noise exposure and cardiovascular and other health problems. Human studies will have provided

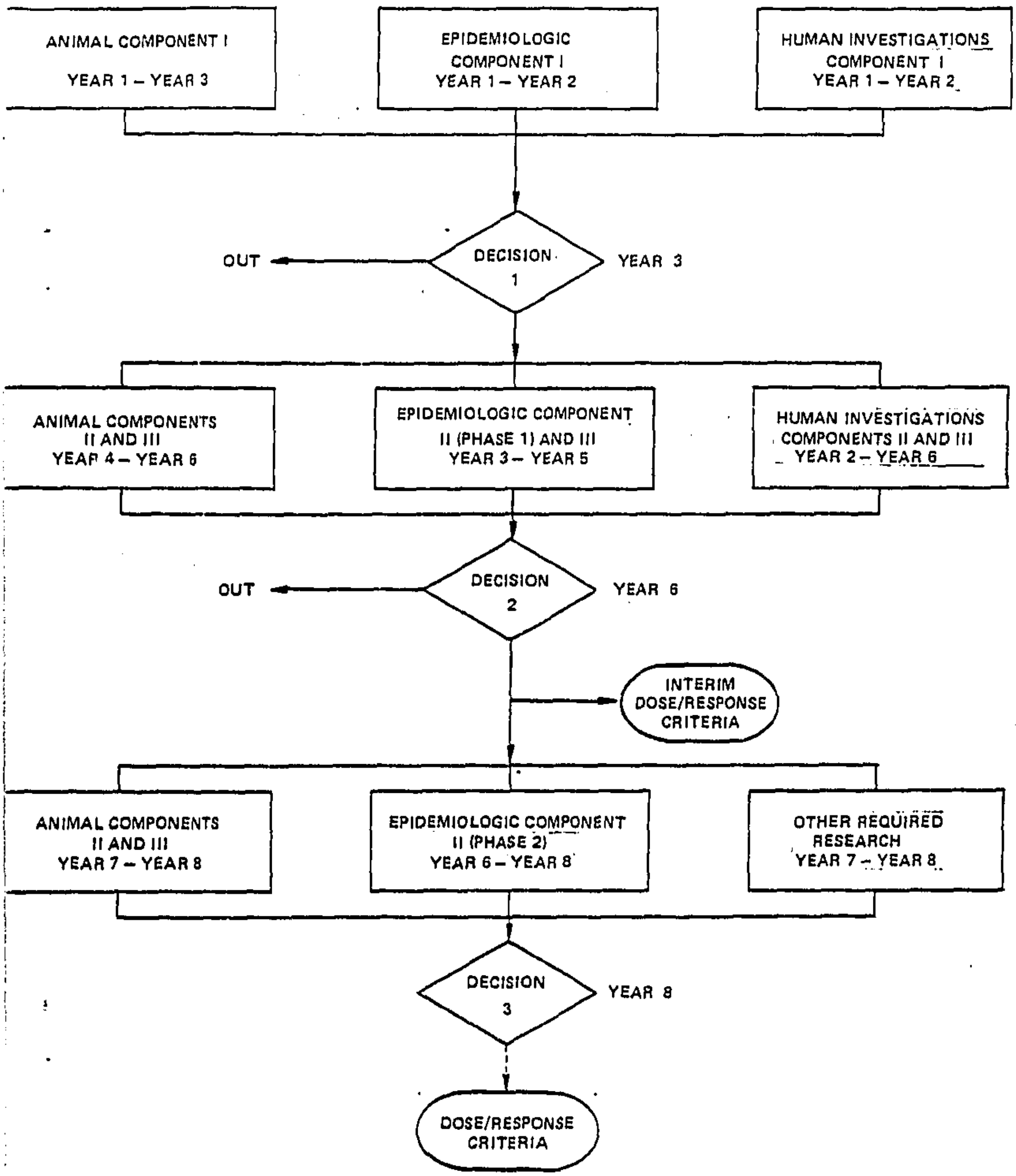

FIGURE 4–1. FLOW CHART OF RESEARCH PROGRAM FOR THE INVESTIGATION OF THE CARDIOVASCULAR EFFECTS OF NOISE

some initial data concerning physiological responses, recovery and adaptation to noise in humans under controlled conditions.

At this juncture, it should be possible to evaluate the full promise of proceeding as planned, or the necessity for making substantial modifications to planned research, retracing previous steps, or stopping research into the cardiovascular effects of noise altogether. The relative contribution to be expected from each of three major research initiatives (Animal Experimental, Epidemiologic, and Human Experimental) should also be known by this point. By the end of Year 3, qualitative information should be available to facilitate empirically founded estimates of the potential extent and magnitude of the cardiovascular effects of noise, and of the level of effort required to fully investigate them.

Decision Point 2 (Year 6)

As the dollar figures portrayed in Table 4-1 indicate, Years 3 to 6 should mark a period of expanded support for research. By year 6, animal and human experimental studies should have provided considerable information on the role and interaction of various acoustic, nonacoustic and predisposing factors. The small scale prospective epidemiologic study, aimed at determining whether or not a causal relationship exists between long-term noise exposure and adverse cardiovascular effects, should have been completed. If the laboratory data are reasonably consistent and reveal "sizeable" effects, and if the epidemiological studies support the establishment of a causal link, then the derivation of interim dose-response criteria would be warranted. The assumption here is that criteria can be offered with less

TABLE 4-1

SUMMARY OF FUNDING LEVELS FOR EACH YEAR FOR EACH RESEARCH INITIATIVE
(Thousands of Dollars)

YEAR	1	2	3	4	5	6	7	8	TOTAL
ANIMAL STUDIES	300	450	500	650	700	700	700	550	4,550
EPIDEMIOLOGICAL STUDIES	200	450	950	1000	900	500	500	500	5,000
HUMAN INVESTIGATIONS AND CLINICAL STUDIES	150	550	500	600	600	600	--	--	3,000
OTHER REQUIRED STUDIES	--	--	--	--	--	400	400	400	1,200
TOTAL	650	1450	1950	2250	2200	2200	1600	1450	13,750 (13.75 Million)

note: To date, EPA has provided approximately 1.2 million dollars in direct support of research on the cardiovascular effects of noise. NIH-NIEHS has contributed approximately 110 thousand dollars, and NIH-NHLBI approximately 150 thousand dollars. All of these funds have been applied to conducting the initial portions of research outlined in this plan.

precision and broader confidence limits if the data reveal large and consistent effects on medically significant cardiovascular parameters. The interim nature of these criteria cannot be over-emphasized, and, regardless of the consistency of the data, research would have to continue in order that something less crude and potentially more protective be developed. Responsible decision-making with respect to noise control alternatives requires an adequate data base from which to extrapolate criteria in which confidence can be placed. In any event, by year 6, a clear picture should have emerged concerning the nature of these effects, their extent and magnitude, and of the direction along which further empirical inquiries should proceed.

Decision Point 3 (Year 8)

By this point, the animal experimental research should have been completed, and three years of data should be available from the large-scale longitudinal research program in which noise would be assessed relative to other cardiovascular risk factors. Other studies deemed necessary in year 6, such as field experiments of cardiovascular and neuroendocrine response, should also be complete or near completion. Thus, it should be possible to develop dose-response criteria for one or several cardiovascular and stress-related parameters. Of course, the most likely candidate is blood pressure. This does not mean that no important questions remain unanswered at this time, but it does mean that useful information will have emerged from a systematic program of animal and human research.

4.2 Research Options

The research initiatives and components outlined in this plan represent the best estimates of the steps deemed necessary to develop dose-response criteria for the cardiovascular effects of noise. During the course of the proposed program, certain alterations in activity will be inevitable and cannot be predicted at this point in time. Other major alternatives, such as discontinuing the research, are obvious from examination of the flow chart shown as Figure 4-1. However, some alternatives can be anticipated at this time. The following paragraphs contain descriptions of these various alternatives and discussions of the major ramifications of pursuing each of the presented alternatives.

It must be remembered that regardless of the amount of funding available or the freedom with which funds can be programmed, certain elements of any research program remain inherently resistant to being compressed or rearranged to any appreciable extent. For example, a study designed to examine health changes over a three year period cannot be compressed into a two or one year period. Although similar studies can be initiated in parallel, true replication usually requires that the findings to be replicated already exist. The necessity and value of replication is usually dictated by the results obtained in the original study.

Option 1. - Omit Retrospective Epidemiologic Study.

The epidemiology feasibility study will provide an objective evaluation of existing literature as well as the feasibility of pursuring various epidemiologic approaches including retrospective studies. The feasibility study may conclude that additional retrospective data are not necessary or that valid data cannot be acquired through this approach. If this is so, further retrospective study should be omitted and the funds transferred to supporting additional animal or human experimental research, or consideration given to initiating the pilot work for the small prospective study in year 1 instead of year 2.

Option 2. - Begin Small Prospective Study Earlier Than Year 3.

With the omission of the retrospective study, it would be possible to begin preliminary work on a prospective study in year 1 as opposed to year 2, and to complete the study in year 4 instead of year 5. The justification for this decision would depend on the findings and recommendations of the epidemiology feasibility study. The disadvantage of deciding to proceed ahead of the original schedule would be the commitment of a large sum of money prior to the availability of substantial data from the animal and human experimental research planned for fiscal years 1 to 3. The advantage of proceeding a year earlier would be completion of the study in year 4 instead of year 5.

Option 3. - Delay "Blood Pressure in Children" Epidemiologic Study.

This study, scheduled for years 3 to 5, could be delayed until the year 6 and year 8 time frame. The advantage of this would be to free additional funds for the purpose of accelerating research progress in the animal and human experimental area. This step could be combined with advancing the prospective study (Option 2), in order that the majority of the information scheduled to be available in year 6 would be available in year 4 or year 5. Accelerating the experimental work would overcome some of the risks of selecting Option 2 alone. The principal ramification of selecting both alternatives 2 and 3 would be that it might be possible to develop an interim dose-response criteria in year 5 or perhaps even year 4. Delay of the "Blood Pressure in Children" Study might mean delaying the investigation of a potentially serious problem.

Option 4. - Delay Animal and Human Experimental Investigations of Susceptibility Differences and Concentrate on Acoustic and Nonacoustic Factors.

This would entail delaying work in Component III of the animal studies and in Component II of the human investigations and clinical studies until approximately year 7. The major advantage of doing this is that funds would become available for accelerating research activity on the acoustic and nonacoustic factors. In the simplest sense, it would appear that this research, i.e., acoustic and nonacoustic factors, is most closely tied to deriving dose-response criteria. Under this alternative, research in Component II (acoustic and nonacoustic factors) of the human studies might be completed in year 4 instead of year 6, and work in Component II (acoustic and nonacoustic factors) of the animal experimental research be completed in year 6 instead of year 8. There is, however, a major disadvantage in selecting this alternative. Some existing evidence suggests that the largest noise effects occur in certain subgroups predisposed or at risk. Cardiovascular risk factor hypotheses hold that such risk factors interact in a multiplicative as opposed to additive fashion. A precaution should be offered against ignoring these potentially important interactions. One runs the risk of severely underestimating the actual impact of noise on the cardiovascular system, if an oversimplified model of action is assumed.

Option 5. - Omit Altogether, or Significantly Reduce the Amount of Human Investigations and Clinical Studies Conducted.

Selection of this option frees additional funds for increased support and acceleration of animal and human epidemiologic research. It is possible that all of most of the animal research could be completed in year 6 or possibly year 5 if this alternative is selected. Selection of this option could be combined with selection of Option 2 and perhaps Option 3 in order to accelerate the epidemiologic program as well. Depending upon the nature of the results, it is possible that more confidence could be placed in an interim dose-response criteria that could be offered as early as year 5. The disadvantage in selecting this option is that human data to parallel the animal data will not be obtained prior to year 5. It should be recognized that questions concerning the interaction of acoustic, nonacoustic, and predisposing factors lend themselves best to human studies. The types of methodologies proposed for inclusion in this program offer an excellent complement to the animal work, and particularly to the epidemiologic work planned. The human investigations permit the exercise of control not available in epidemiological research and acquisition of data not obtainable from animal experiments.

Data from the human experimental work will feed directly into the epidemiologic aspect of the program. The relative success of the human experimental research will also influence the amount of animal research that will be required, and consequently the extent to which conclusions and ultimately criteria must be founded on non-human data.

4.3 Rush Progam

Simultaneous selection of Option 1 (omission of retrospective study), Option 2 (acceleration of small prospective study), and Option 3 (delay of "Blood Pressure in Children" study) would form the basis of a "Rush Program" of research. Selection of these options would have to be accompanied by increased level of support for animal and human experimental work in the time period of years 1 to 4. Depending on the magnitude and consistency of results, it might be possible to forward interim criteria in year 4 or 5 as opposed to year 6 as specified in the flow chart (Figure 4-1). This does not imply that all the work required for the development of refined criteria would have been completed by this date, only that more confidence might be placed in the interim criteria.

Completion of this Rush Program would require funds in excess of those originally estimated for years 1 to 4. Approximate levels of support are presented in Table 4-2. As is apparent from the table, in excess of 8.3 million dollars between fiscal years 1 and 4 would be needed for such a Rush Program as compared to 6.3 million in the original program.

There are several disadvantages or risks associated with pursuing a Rush Program: Mid-course corrections could not easily be made under such a program, nor could advantage be taken of important methodological refinements. Such an accelerated program would benefit only marginally from the synergistic effect of a multifaceted, time-phased program of research. Such a program would provide no margin for error. Pursuit of a Rush Program requires the capability to map out the specific experimental and epidemiologic protocols and time-phasing of studies for virtually the whole program immediately. The state of previous research does not permit that level of

TABLE 4-2

SUMMARY OF FUNDING LEVELS FOR "RUSH PROGRAM"
BY RESEARCH INITIATIVE
(Thousands of Dollars)

YEAR	1	2	3	4	TOTAL
ANIMAL STUDIES	950	950	950	950	3800
EPIDEMIOLOGICAL STUDIES*	200 (700)	700 (750)	750 (650)	650 (0)	2300 (2100)
HUMAN INVESTIGATIONS AND CLINICAL STUDIES	600	600	600	600	2400
TOTAL	1750 (2250)	2250 (2300)	2300 (2200)	2200 (1550)	8500 (8300)

*Two choices are presented. Data collection for Phase 1 of the Prospective Analysis could be initiated in either year 2 or year 1. The Yearly Figures if the year 1 choice is selected are shown in parentheses.

specificity with a high level of confidence. The relative paucity of previous systematic research, the conflicting nature of some findings, and the extent of methodological criticism levied against some of the research all contribute to increasing the risk associated with pursuing a compressed research program.

4.4 Recommendations

The preceding options represent some of the major choices available in carrying out this research program within the general time and funding estimates given. The following recommendation is offered: It is recommended that the program begin with a balanced attack on the problem. That is, time-phased efforts should be made in each of the three investigative approaches: animal experimental, epidemiologic, and human investigations and clinical studies. The program should be allowed to build its own momentum.

The year 3 decision point is particularly important because, for the first time, enough data should be available to make a reasoned assessment of the potential magnitude and extent of the cardiovascular effects and of the full potential of pursuing an aggressive criteria-oriented program of research. Based on the initial results of research carried out between years 1 and 3, a decision should be made as to the relative potential for contributions to the development of dose-reponse criteria offered by each of the three approaches or initiatives. Scientific merit should be the primary evaluation factor, with consideration also given to time and cost variables. Subsequent funding should be allocated on the basis of empirical data, not *a priori* speculation. <u>If large and consistent effects emerge early in the program, the potential health implications require that support be increased</u>

to the extent necessary in order that criteria be developed as soon as possible.

Careful scrutiny should be applied to the results of the epidemiologic feasibility study. This information should permit a reasoned decision on the precise nature and phasing of future epidemiologic research. Budget constraints may necessitate that consideration be given to reprogramming funds allocated for the blood pressure in children study scheduled to be conducted in years 3 through 5 (Option 3) To the extent that these funds would be needed, Option 3 should be considered at that time.

5. SUMMARY

The research program which has been outlined in the preceding sections represents a multi-faceted, time-phased program of study. Interest is in the examination of the relationship between noise exposure and adverse cardiovascular effects, taking into consideration the role and interaction of various acoustic, nonacoustic, and predisposing factors.

The development of criteria for the cardiovascular effects of noise is viewed as being a multi-disciplinary research program requiring input from acoustics and several areas of biomedical and behavioral science. Building upon what is known about the physiological effects of noise and about hypertension and the cardiovascular disease process, planned research should include initiatives in the animal experimental, human epidemiologic, and human experimental areas.

Each initiative is designed to reflect graduated scientific effort. Initial concern is with the establishment of the relationship of noise to cardiovascular effects, and with the assessment of the extent and magnitude of the relationship. This is followed by investigation of the circumstances under which these effects are most pronounced. Research elements within the initiatives are oriented toward the generation of dose-response criteria. There is also an intent to design studies within each initiative that will yield findings which impact and/or complement the findings obtained in the other initiatives.

The research program contains three major decision points. These decision points serve to mark progress and provide opportunities for program redirection and reemphasis. Decision Point 1 (year 3) allows for initial estimates of the magnitude and extent of the cardiovascular effects of noise, and of the level of effort required to fully investigate them. By Decision Point 2 (year 6) information should be available to make a quantitative assessment of the effects of noise on selected cardiovascular responses and to possibly forward interim dose-response criteria. The third decision point occurs just prior to the generation of more refined dose-response criteria (year 8).

The advantages and disadvantages of pursuing several options within the program are discussed. Although a "rush program" is considered, the recommendation is made for a more graduated program on the basis of both the current state of knowledge concerning the cardiovascular effects of noise and the complex nature of the research involved. If large and consistent findings are obtained in the early stages of the program, then the level of support should be increased to the extent necessary to facilitate the development of criteria in the shortest possible time.