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Soviet-American Cooperation in Environmental Health Science

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Introduction

U.S.-U.S.S.R. cooperation in the field of environmental health was included as one of the initial three priority areas in the February, 1972 exchange of letters between U. S. Secretary of Health, Education and Welfare Elliott Richardson and U.S.S.R. Minister of Health Boris Petrovsky, and in the five-year Agreement for Cooperation in the Fields of Medical Science and Public Health, signed in Moscow, May 24, 1972. Prior to 1972, contacts between American and Soviet scientists and officials responsible for research on problems of environmental health were informal and infrequent. The fact that environmental health was included as one of the three priority areas, along with cardiovascular diseases and cancer, reflects the recognition by both sides of the important role which environmental factors play in human health, and the fact that understanding and controlling the effects of environmental pollution has become an international problem.

Since 1972, the coordinators for the environmental health priority area have been, for the U. S., Dr. D. P. Rall, Director of the National Institute of Environmental Health Sciences, and for the Soviet side, Dr. P. N. Burgasov, Deputy Minister of the U.S.S.R. Ministry of Health and Dr. G. I. Sidorenko, Director of the A. N. Sysin Institute of General and Communal Hygiene.

The U.S. and Soviet Coordinators and Problem Area Leaders had their first organizational meeting in the U.S. in January, 1973. Initially, the focus of joint research was on exploring and developing common methodology for the study of the effects of environmental pollutants entering biological systems through inhalation, oral ingestion, or both routes simultaneously, which became the three problem areas under which joint research was organized. It was agreed initially to conduct joint work on eight topics under the three problem areas. Joint studies and exchange visits were carried out during 1973 and 1974 with the results of the first two years of collaborative research being presented at the First Joint Symposium in Riga, Latvia in December, 1974. The papers presented at the symposium were published in the United States (in Environmental Health Perspectives, Volume 13, 1976) and the Soviet Union. The symposium was also the occasion for the development of joint work plans for 1975-76. In December, 1976, the scientific results for the period 1975-76 were presented at the Second Joint Symposium held in Marineland, Florida. The papers from this symposium are published in this volume of EHP. Research protocols for joint work for the period 1977-78 were agreed upon during the symposium.

During the first five years of cooperation in the environmental health priority area, 33 American scientists from 14 different institutions made 60 visits to the U.S.S.R. (for a total of 754 man-days); during the same period, 33 Soviet scientists from 14 different institutions have made 48 trips to the U. S. (for a total of 912 man-days).

In 1975, a fourth problem area dealing with the biological effects of physical factors in the environment was added. In 1976, the cooperative effort was reorganized to address the problems of environmental health from a different perspective. Currently, cooperative efforts are aimed at the development of methods for the quantitative evaluation of the biological effects of environmental

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chemical agents; development of methods for predicting the biological effect of environmental chemical agents; study of the long-term biological effects of environmental chemical agents; and study of the biological effects of physical factors in the environment.

Problem Area Activities and Achievements

The four problem areas of the environmental health priority area represent some of the most difficult challenges in understanding and predicting the effects of environmental pollutants on human health. One of the principal aims of environmental health research is to develop information which can be used by appropriate regulatory authorities in the establishment of environmental standards for the protection of public health and occupational groups.

Problem Area 1 Development of Methods for the Quantitative Evaluation of the Biological Effects of Environmental Chemical Agents

The success of national efforts to regulate chemical agents in the environment must eventually depend upon the development of adequate scientific methods for the quantitative measurement of the biological effects of those agents. This problem is currently being pursued through joint research on four topics, two of which are recent additions to the cooperative program, the remaining two having been the subject of joint research since 1973.

One of the practical problems encountered in assessing the effect of atmospheric pollutants on people is the fact that exposure to these pollutants typically varies in concentration from time to time during the day or week as a result of different rates of emission into the environment and changing meteorological influences. In setting standards to protect public health from the hazards of exposure to atmospheric pollutants, it is essential to know the significance of these varying exposures. In joint research on the comparative assessment of the effect of continuous and intermittent exposure to atmospheric pollutants D. L. Coffin and D. E. Gardner (U. S. Environmental Protection Agency) and M. A. Pinigin (A. N. Sysin Institute of General and Communal Hygiene) have conducted experiments aimed at developing a quantitative relationship which could be used to calculate the biological effects of exposure to varying concentrations of atmospheric pollutants (*1–6*).

Based on inhalation experiments in animals, Coffin, Gardner, and Pinigin have developed and verified a mathematical expression of the dose-time-effect relationship for a number of atmospheric chemicals. Soviet scientists showed this relationship for a number of chemicals, benzene and sulfur dioxide among them, using a variety of biological parameters. American scientists showed a similar association for nitrogen dioxide by means of the infection-inhalation model for both continuous and intermittent exposure regimens. The conclusion from the study of intermittent exposure is that this is an important factor to be considered in the setting of standards for atmospheric pollutants.

The often subtle effects of low levels of pollutants on behavior and the central nervous system are becoming increasingly recognized as being among the early signs of the effects of environmental pollution. To develop generally accepted methods for studying the effect of environmental factors on the central nervous system and behavior, B. Weiss (University of Rochester) and A. I. Bokina (A. N. Sysin Institute of General and Communal Hygiene) undertook a project to compare methods employed in the United States and the Soviet Union, which have different histories of the development of behavioral toxicology, for the study of the behavioral effects of environmental toxicants. Carbon disulfide (CS_2), historically recognized as a potent neurotoxin, was selected as the joint object of study for the beginning phases of the collaboration. The American side studied effects on operant behavior in pigeons and motor coordination and control in monkeys. The Soviet side studied effects on rabbits and humans, emphasizing electrophysiological methods, particularly visual evoked potentials. The studies by Weiss and co-workers (*7–9*) indicated that CS_2 effects on pigeon behavior might be due to inhibition of the enzyme dopamine-β-hydroxylase; a drug known to inhibit this enzyme produced equivalent results on behavior. More recent studies indicate that the nonhuman primate is a more sensitive organism than the pigeon. The studies by Bokina et al. (*10, 11*) indicate that central nervous effects take place at extremely low concentrations of CS_2 in short-term exposures.

Underlying most studies of the action of environmental agents on biological systems are a variety of biochemical methods designed to measure specific effects. In a new joint topic, M. D. Waters (U. S. Environmental Protection Agency) and R. V. Merkuryeva (A. N. Sysin Institute of General and Communal Hygiene) will assess the use of different biochemical methods for the study of the mechanisms of action of environmental agents on biological systems. Initially, joint research will be aimed at comparing the results from *in vivo* and *in* *vitro* studies of the effects of various chemicals with the aim of determining how well the biochemical data correlate in two approaches.

Because of the growing evidence of the relationship between the mineral composition of drinking water and the incidence of cardiovascular disease, another new topic, concerned with assessing the biological effect of different levels of mineralization of desalinated drinking water has been initiated by R. R. Suskind and H. G. Petering (University of Cincinnati) and Yu. A. Rakhmanin and A. I. Bokina (A. N. Sysin Institute of General and Communal Hygiene). Joint research on this topic will aim to develop information on permissible and optimal levels of total salinity in hard drinking water. The cooperative studies will provide new data about the specific aspects of the biological effects of demineralized drinking water on biological systems (*12*).

Problem Area 2
Development of Methods for Predicting the Biological Effects of Environmental Chemical Agents

Because of the large and increasing number of different chemical compounds introduced into man's environment each year, as well as the enormous number of compounds to which man is already exposed, it is impossible to perform all of the costly and time consuming toxicological tests that would be needed to demonstrate the safety of these compounds, singly and in combination. It is essential, therefore, to develop acceptable methods for predicting the potential hazards of chemicals before they are introduced into the environment and to speed up the evaluation of the safety of those compounds already in the environment.

Several joint research topics have been developed to approach this problem from different angles.

One of the most challenging problems facing environmental health scientists is understanding and predicting the effects caused by two or more chemicals acting simultaneously on an organism, sometimes through a single route of exposure (e.g., inhalation) to give a combined effect, and sometimes through multiple routes (e.g., inhalation and ingestion) to give complex effects. B. D. Goldstein (New York University Medical Center) and V. R. Tsulaya (A. N. Sysin Institute of General and Communal Hygiene) have been working on developing methods for predicting the combined and complex effects of chemicals. The study of the effects of multiple pollutants inhaled simultaneously is a relatively unexplored area of air pollution research, despite the fact that it is recognized that the toxicity of such mixtures may not be predictable on the basis of response to the individual components. The U. S. side studied the combined effects of ozone and nitrogen dioxide in an *in vitro* test system utilizing human red cells and *in vivo* in rats (*13, 14*). Studies showed that the effects of these two pollutants vary from protective to synergistic, depending on the pollutant concentration, duration, and sequences of exposure, as well as on the parameter assayed. This resulted in the preliminary conclusion that it might be misleading to estimate the combined effects of ambient levels of two pollutants by extrapolating from a study in which the effects of a single dose of each was compared with effects occurring after combined exposure to the same doses of both pollutants. The U. S. side is extending these observations to *in vivo* studies in rats. The Soviet side studied the combined effect of several chlorinated hydrocarbons in mice and rats. They have found that the effects of the action of the mixtures of these gases at high and low concentrations do not differ, and the magnitude of the combined effect is the sum of the effect of the gases separately (*15, 16*).

Present methods in use for predicting the toxicity of environmental chemicals by studies in laboratory animals are slow to give results and are costly to conduct. In order to develop more rapid experimental methods for predicting the general toxic effects of chemical compounds, joint work was initiated by V. H. Freed (Oregon State University) and S. A. Shigan (A. N. Sysin Institute of General and Communal Hygiene). The objectives of cooperative work on this topic were to develop and evaluate rapid and short-term methods of assessing toxicity and relating them to standards and to investigate the correlation of physicochemical properties to biological activities as a means of predicting toxicity. The initial empirical tests of toxicity utilized several organochlorine compounds and organophosphates. Parallel studies were concerned with the relation of various physicochemical properties of the compounds to their accumulation in biological systems and subsequent toxicity. These studies have demonstrated a good correlation between the rapid short-term tests and the accumulation and toxicity to be expected of a compound. These studies are significant in that they permit more rapid evaluation of toxic hazard and indicate permissible levels of exposure and allow for some early inferences or predictions of possible biological activity (*17–20*).

Because organochlorine pesticides are widely used in the United States and the Soviet Union, joint experiments were undertaken to elucidate some of the more subtle biological responses associated with exposure to toxaphene. D. B. Peakall (Cornell University) and U. A Kuzminskaya (All-Union Scientific Research Institute of the Hygiene and Toxicology of Pesticides, Polymers and Plastics) have evaluated the effects of toxaphene on the levels of several enzymes and metabolites present in rat serum and urine as well as tissues including liver, brain, and heart. Their findings indicate the importance of associating altered enzyme levels with concomitant changes in related metabolite levels in order to evaluate the physiological consequences of exposure to organochlorines such as toxaphene (*21–24*).

Even when good toxicological data can be obtained from experiments with laboratory animals, a major problem remains in relating, or extrapolating, the results to the human situation. In order to improve the scientific base for extrapolation of laboratory animal data to man, R. L. Dixon (National Institute of Environmental Health Sciences) and G. N. Krasovskii (A. N. Sysin Institute of General and Communal Hygiene) undertook a joint effort aimed at understanding strain and species differences between biological organisms with regard to toxicological response. Soviet scientists have shown that the toxicity parameters of compounds and the biological constants of mammals correlate with body weight and other biological parameters enabling the development of a computational method for extrapolating toxicologic data from animals to the "average" man (*25*).

American scientists have examined the quantitative predictiveness of preclinical studies of anticancer drugs using dogs and monkeys for man, in particular, the relationship between the maximum tolerated dose (MTD) in the dog and monkey, and the more sensitive of the two species, and clinical observations. The relative effectiveness of using doses expressed on the basis of body weight (mg/kg) and body surface area (mg/m^2) was studied. A method was introduced to assess the "statistical risk" associated with the extrapolation of the initial clinical dose from experimental animal data. These same data have been extended theoretically to the total population and toxic chemicals in general (*26*).

One special class of chemicals of concern to environmental health scientists, because of their increasing prevalence in the biosphere, is metals. G. N. Krasovskii studied the relationship of the general toxic and gonadotoxic effects of cadmium, boron, and aluminum on rats (*27, 28*). It was shown that the gonadotoxic effect of cadmium is manifested on the same level (3 mg/kg body weight) as the general toxic effect. The gonadotoxic effect of boron is dominant and is manifested at a lower level (6 mg/kg body weight) than the general toxic effect (20 mg/kg).

Studies by R. L. Dixon attempted to evaluate the reproductive toxicity of cadmium, aluminum, and boron and investigate the mechanism of toxicity in the rat (*29, 30*). These initial studies, utilizing a variety of methods to assess the reproductive toxicity of environmental substances in male animals, suggest that cadmium, aluminum and boron at the concentrations and dose regimens tested are without significant reproductive toxicity.

One promising method for the rapid prediction of the biological effects of environmental chemicals is based on studies of the correlation of the structure of chemical compounds with biological activity. In order to develop methods for predicting the biological effect of chemicals on the basis of their chemical structure, V. H. Freed (Oregon State University) and N. G. Andreeshcheva (A. N. Sysin Institute of General and Communal Hygiene) developed a joint study of the biological activity of substituted benzenes. Correlations of biological activity were found with a number of physical properties, but three are of particular significance; namely, vapor pressure, partition coefficient, and out-of-plane vibration as indicated by infrared absorption. These studies provide a basis of evaluation and anticipation of biological activity of derivatives of mono aeromatic compounds (*31, 32*).

Problem Area 3
Study of the Long-Term Biological Effects of Environmental Chemical Agents

Among the most difficult problems in assessing the effects of chemical agents introduced into the environment is the determination of their potential hazards as a result of long-term exposures to low doses of these compounds. Of particular concern are the agents which lead to the development of cancer, cardiovascular effects, and birth defects which are among the most significant health problems facing the world's population. Several joint topics aim at a study of these problems.

R. E. Albert and B. Altshuler (New York University Medical Center) and N. Ya. Yanisheva (A. N. Marzeev Institute of General and Communal Hygiene) have undertaken a study of the dose-time-effect relationship with respect to different routes of administration of the carcinogen benzo(a)pyrene (*33–35*). The objective of this long-term study is to obtain a better understanding of the temporal aspects of tumor formation for characterizing dose-response relationships in terms of incremental cancer incidence and age of cancer occurrence.

These relationships could then be the scientific basis for formulating standards for exposure to environmental carcinogens.

The role of environmental factors as causative agents in producing birth defects and interfering in human reproduction has come under increasing scrutiny. A study of the teratogenic and embryotoxic effects of pesticides and other chemical substances has been undertaken by R. E. Staples (National Institute of Environmental Health Sciences) and L. V. Martson (All Union Research Institute of Hygiene and Toxicology of Pesticides, Polymers, and Plastics). This joint work was initiated with the study of the teratogenic potential of the organophosphate pesticides, Dipterex and Imidan in the rat. The U. S. side looked at the consequences of administration of the pesticides by gavage and by diet. The Soviet side studied the effects caused by inhalation and gavage. In the U. S. it has been determined that Dipterex is teratogenic in the rat, hamster, and mouse, and that Imidan is not teratogenic in the rat even when administered at toxic dose levels (*36, 37*). Although one-quarter of the world's supply of Dipterex is used in the United States, its potential teratogenicity was not previously known. The Soviet side also found Dipterex to be teratogenic in the rat and in the hamster. The Soviets found Imidan to be very teratogenic in the rat when given by gavage (*38*) but the Imidan used for the Soviet study was not the same as used in the U. S. In a subsequent study with a sample synthesized in the Soviet Union, Imidan was found not to be teratogenic in the rabbit.

In a new topic under this problem area, R. R. Suskind and H. G. Petering (University of Cincinnati) and I. V. Sanotsky (Institute of Industrial Hygiene and Occupational Diseases) have initiated a study of the long-term effects of chemical compounds on the cardiovascular system. The aim of collaborative research on this topic is to determine the role of microconcentrations of chemical pollutants which produce cardiovascular change, to elucidate possible mechanisms of adverse changes, and to determine safe levels of exposure for such chemical pollutants. Initially, this effort will be concerned with the effect of carbon disulfide, carbon monoxide, and heavy metals such as cadmium and lead. Using morphological, physiological, and biochemical methods, an attempt will be made to establish the thresholds of the adverse effect and the selective action level of these compounds on the cardiovascular system.

Another new topic in the discussion stage involving G. N. Wogan and S. R. Tannenbaum (Massachusetts Institute of Technology) and N. P. Napalkov (Institute of Oncology), P. A. Bogovsky (Institute of Experimental and Clinical Medicine) and V. S. Turusov (Oncologic Scientific Center) is concerned with the development of studies on the biological effect of nitrosamines from various sources. Nitrosamines are a class of carcinogenic compounds which have become of increasing concern to environmental health scientists because of the discovery of their presence in water and the atmosphere. Other nitrosamines are found in the food supply as the result of the use of nitrogen fertilizers. Nitrosamines can also be formed in the human stomach by conversion of the nitrates used as a food preservative.

Problem Area 4
Study of the Biological Effects of Physical Factors in the Environment

While environmental health scientists and public health hygienists have been largely concerned (and properly so) about the effects of chemical compounds in the environment, another class of factors—physical factors—is becoming of increasing concern. Physical factors typically consist of energy transmitted to biological systems in the form of heat, light (both visible and UV), noise, and ionizing and non-ionizing radiation. Initially, joint efforts in this problem area, which was added to the cooperative program in 1975, have focused on the biological effects of nonionizing radiation; in particular, effects of microwave radiation and of static and low frequency electromagnetic fields. Radiation from these sources are becoming of increasing concern as the number and extent of their sources grows. Microwave fields are emitted by radars, communication devices, and microwave ovens while strong static and low frequency electromagnetic fields are found around high voltage direct and alternating current electric transmission lines.

Initial collaborative efforts on the microwave effects problem have been conducted by D. I. McRee (National Institute of Environmental Health Sciences), A. W. Guy (University of Washington), R. Adey (University of California at Los Angeles), M. L. Shore (Food and Drug Administration), J. A. Elder and M. Gage (Environmental Protection Agency) and M. G. Shandala, M. I. Rudnev, L. K. Yershova and N. P. Los (A. N. Marzeev Institute of General and Communal Hygiene). This joint effort is aimed at elucidating the potential health hazards associated with long-term exposures to low doses of microwaves.

A difference in the type of research being done in the Soviet Union and the United States was evident from the beginning of joint work. The Soviet research was performed at very low levels of exposure for long periods of time. Since the beginning of collaboration, the U.S. side has added additional projects having longer durations of exposure, and the Soviet side has increased their power density exposure levels.

During the first year of the program, the Soviet side reported (*39*) effects on rabbits and rats due to microwave exposure at power densities of 10 to 500 $\mu W/cm^2$ and exposure durations of 7 hr/day, 5 days per week for 3 months. They measured changes in EEG in rabbits, and alterations in behavior and immunological and cytochemical parameters in the blood of rats. The U.S. studies (*40*) at the higher exposure levels in general showed no effects unless the levels were high enough to provide heating of the specimens. Several exceptions to these findings were noted. Adey measured increased calcium efflux from brain tissue at microwave fields modulated near brain wave frequencies. Guy and McRee have measured a suppression of immunological response in rabbits exposed to 10 mW/cm^2 for a six-month period. Gage measured significantly decreased performance in rats following exposure to 15 mW/cm^2 and above. The significance of these findings indicates that additional attention must be given to methodology and experimental design.

Collaboration on studies of the effects of static and low frequency electromagnetic fields is in the early stages of development. An exchange of reviews of national scientific literature on this topic has taken place and a joint workshop has been convened to review the state of knowledge on this topic and propose joint work on outstanding problems.

Other Activities and Achievements

At an early point in the collaboration in the environmental health priority area, the need for a bilingual glossary of the specialized scientific terms in use in both countries in the area of environmental health was recognized. With the contributions and help of environmental health scientists and language specialists from both sides, the first edition of a glossary of terms was completed in 1975.

Prospects for Future

The first five years of Soviet-American collaboration in the environmental health priority area have opened up communications between both sides on a wide range of scientific topics critical to understanding and predicting the effect of environmental contaminants on human health. The main themes of collaboration developed during the first five-year period will be continued. It is expected that a number of research topics will produce information of direct relevance to the need to establish standards for the protection of the health of public and occupational groups from agents polluting the environment. Other studies will result in significant contributions to understanding the basic biological and biophysical processes which occur as environmental agents interact with biological systems. In the long run, it is expected that this knowledge will lead to an improvement of methods for predicting and preventing the adverse effects of agents which may be introduced into man's environment.

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