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OCCUPATIONAL CARCINOGENESIS PROGRAM

JULY 1, 1975 — SEPTEMBER 30, 1976

NIOSH

National Institute for Occupational Safety and Health

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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In recent years, new cancer cases in the U.S. have been developed at the rate of 600,000 per year resulting in a cancer death rate in excess of 350,000 per year. Spokesmen from the National Cancer Institute have stated that 80-90 percent of these cancers can be traced to an environmentally-induced origin; and a past Director of the National Institutes of Health has stated that most known environmental carcinogens are a result of our increased agricultural and industrial technology. In the past, these considerations have not been appropriately reflected in Federal priorities and the allocation of research resources for prevention in contrast with resources for the diagnosis and treatment of human cancer.

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NIOSH OCCUPATIONAL CARCINOGENESIS PROGRAM

First Year Report
July 1, 1975 - September 30, 1976

U.S. DEPARTMENT OF HEATLH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health
Rockville, Maryland 20852

October 19, 1976

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First Year Report of the NIOSH
OCCUPATIONAL CARCINOGENESIS PROGRAM
Covering Fiscal Year 1976 and the Transition Quarter

INTRODUCTION

In recent years, new cancer cases in the U.S. have been developed at the rate of 600,000 per year resulting in a cancer death rate in excess of 350,000 per year. Spokesmen from the National Cancer Institute have stated that 80-90 percent of these cancers can be traced to an environmentally-induced origin; and a past Director of the National Institutes of Health has stated that most known environmental carcinogens are a result of our increased agricultural and industrial technology. In the past, these considerations have not been appropriately reflected in Federal priorities and the allocation of research resources for prevention in contrast with resources for the diagnosis and treatment of human cancer.

With the belief that most known environmental carcinogens are the result of modern technology, it must be concluded that the bulk of human exposure to high concentrations of chemical carcinogens and radiation will occur at the workplace. Therefore, it is not surprising that the interest of many cancer researchers has turned to the occupational environment. In order to provide a focus for Federal research on cancer in the occupational setting, NIOSH developed an "Expanded Occupational Carcinogenesis Program" for inclusion in the DHEW Forward Plan for Health for FY 1976-1980.

The NIOSH Occupational Carcinogenesis Program is a comprehensive effort including surveillance, industrywide studies, and laboratory research. The NIOSH program in FY 75, before the implementation of the expanded Occupational Carcinogenesis Program, was funded at $1.8 million. In FY 76, $6.9 million were allocated to implementing the program. To make the transition from a very modest program in FY 75 to a more substantial and comprehensive program in FY 76, a Task Force was assembled with representatives from NIOSH's operating divisions. A plan was developed by this group based on the allocation of resources to three areas: Recognition, Evaluation (industrywide studies and laboratory studies), and Control. Table I indicates the resources planned for these areas and the funds obligated (to be expended). Table II shows planned and obligated funds for the Transition Quarter (T.Q.). One category (Facilities Modification) has been added to account for funds spent for construction of carcinogens laboratories. The plan also listed specific projects which were to be carried out by NIOSH divisions during FY 76.

The rationale for categorical separation of the Carcinogenesis Initiative into program phases of Recognition, Evaluation, and Control are detailed in the Carcinogenesis Task Force Report. It is generally recognized that the occupational environment is most likely the first place where carcinogenic problems will be identified, and the authority for "right of entry" gives NIOSH a unique opportunity to lead the way in characterization and prevention of occupationally derived cancer.

Table III lists the projects developed for the plan. The projects are grouped according to the conceptual program elements of Recognition, Evaluation, and Control. Resources are shown for each project title in the form of man-years of effort, positions, and total dollar funds obligated. In most cases, there were more positions than man-years. This apparent discrepancy is to account for the lag in hiring personnel after authority was obtained to fill allocated positions. A separate listing of T.Q. projects is not provided since these were the same as for FY 76. However, a summary of allocations and obligations for the T.Q. is available in Table II.

TABLE I

NIOSH Carcinogen Task Force Allocation and Obligation - FY 76

Activity	Allocated				Obligated	
	Positions	%	Dollars	%	Dollars	%
I. Recognition	17	13.8	789,000	11.5	659,599	12.2
A. Surveillance	14	11.4	636,000	9.3	312,252	5.8
B. Assessment	3	2.4	153,000	2.2	347,347	6.4
II. Evaluation						
A. Industrywide Studies	57	46.3	2,404,160	35.1	1,909,206	35.4
1. Studies by Industry	24	19.5	872,960	12.7	791,927	14.7
2. Studies by Agents	33	26.8	1,531,200	22.4	1,117,279	20.7
B. Laboratory Studies	30	24.0	2,140,817	31.2	1,170,119	21.7
1. Developmental Res	20	16.0	1,193,448	17.4	445,402	8.3
2. Experimental Res	10	8.0	947,369	13.8	724,717	13.4
III. Control	21	17.1	1,518,023	22.2	1,652,770	30.7
A. Engineering	14	11.4	1,175,743	17.2	1,244,760	23.1
B. Medical	0	0	0	0.0	0	.0
C. Technology Transfer	7	5.7	342,280	5.0	408,010	7.6
	125	100	6,852,000	100	5,391,694	100

TABLE II

NIOSH Carcinogen Program Allocation and Anticipated Obligations
for the Transition Quarter

Activity	Allocated		Obligated	
	Dollars	%	Dollars	%
I. Recognition	197,250	7.3	68,598	1.8
A. Surveillance	159,000	5.9	34,013	.9
B. Assessment	38,250	1.4	34,585	0.9
II. Evaluation				
A. Industrywide Studies	601,040	22.2	1,685,520	44.6
1. Studies by Industry	218,240	8.0	1,056,171	28.0
2. Studies by Agent	382,800	14.2	629,349	16.6
B. Laboratory Studies	535,204	19.7	555,938	14.7
1. Developmental Res	298,362	11.0	477,323	12.6
2. Experimental Res	236,842	8.7	78,615	2.1
III. Control	379,506	14.0	471,567	12.5
A. Engineering	293,936	10.8	353,632	9.4
B. Medical	0	0	0	0
C. Technology Transfer	85,570	3.2	117,935	3.1
IV. Facilities Modification	1,000,000	36.9	1,000,000	26.4
Total	2,713,000	100.0	3,781,623*	100.0

*$920,000 provided by the National Cancer Institute in support of three contract studies.

TABLE III - NIOSH '76 OCCUPATIONAL CARCINOGENESIS INITIATIVE

Occ. Carcinogenesis Program Project No.	Activity & Project Titles	MY Efforts	Allocations Positions	Allocations Dollars	Obligations Dollars
	I. Recognition	0.0	17.0	789,000	659,599
	A. Surveillance	0.0	14.0	636,000	312,252
1	1. Identification of High Risk Occupations for Cancer		4.0	300,000	154,150
2	2. Retrieval of Morbidity Data from Automated Systems		2.0	36,000	52,102
3	3. Occupational Carcinogenesis Intelligence		6.0	200,000	57,500
4	4. Inventory of Agents and Exposures		2.0	100,000	48,500
	B. Assessment	0	3.0	153,000	347,347
6	1. Current Intelligence System		1.0	73,000	125,885
7	2. Research Analysis & Priority Setting		2.0	80,000	221,462
	II. Evaluation - Industrywide Studies	49.2	57.0	2,404,160	1,909,206
	A. Studies by Industry	19.3	24.0	872,960	791.927
8	1. Printing Trades		1.0	154,000	4,700
9	2. Mortality of Dairymen	0.4	0.0	100,000	162,424
10	3. Uranium Mill and Miner Studies	0.9	1.0	0*	24,000
11	4. Plywood, Pulp, and Paper Mill Studies	1.0	2.0	150,000	28,000
12	5. Coal Gasification Study	2.3	2.0	19,100	25,470
13	6. Phosphate Fertilizer Industry	2.4	3.0	75,000	63,788
14	7. Retrospective Mortality & Morbidity of Pesticide Formulators	0.1	0.0	461,000	43,013

Occ. Carcinogenesis Program Project No.	Activity & Project Titles	MY Efforts	Allocations Positions	Allocations Dollars	Obligations Dollars
	8. Metal Industries				
15	a. Long-term Mortality Experience of Steelworkers	0.6	1.0	17,460	7,077
16	b. Mortality of Antimony Smelter	2.6	3.0	100,000	78,273
17	c. Mortality Study of Beryllium Workers	0.5	0.0	17,500	131,488
18	d. Mortality of Cadmium Smelter Workers	2.0	2.0	39,900	58,514
19	e. Mortality Study of Lead Industries	2.0	1.0	50,000	165,180
	B. Studies by Agent	29.9	33.0	1,531,200	1,117,279
20	1. Pilot Study of Occupational Exposure to Ionizing Radiation	0.4	0.0	35,000	61,307
21	2. Occupational Benzene Exposure	2.8	4.0	150,000	133,500
22	3. Evaluation of Five Suspect Carcinogens: Epichlorohydrin, Fluorohydrocarbons, Vinylhalides, and Styrene Butadiene	7.2	7.0	401,800	92,550
	4. Chlorinated Hydrocarbons				
23	a. Study of Vinyl Chloride Workers	0.8	1.0	61,400	23,950
24	b. Bischloromethyl ether in Selected Work Environment	0.5	1.0	19,000	54,201
25	c. Other (Trichloroethylene, Poly Chlorinated Biphenyls, Chloroprene, Benzyl Chloride. & Methyl Chloride)	8.2	8.0	500,000	509,631
	5. Fibrous Materials				
26	a. Cofactors in Etiology of Asbestos Associated Cancer	6.2	8.0	250,000	147,720
27	b. Carcinogenicity potential of talc	3.8	4.0	114,000	94,420

Occ. Carcinogenesis Program Project No.	Activity & Project Titles	MY Efforts	Allocations Positions	Allocations Dollars	Obligations Dollars
	II. Evaluation - Laboratory Studies	22.5	30.0	2,220,817	1,170,119
	A. Developmental Research (Methods, Sampling Analysis)	11.3	20.0	1,193,448	445,402
28	1. Sampling & Analytical Methods for Carcinogenic Compounds: Organic	4.0	9.0	395,000	186,178
29	2. Sampling & Analytical Methods for Carcinogenic Compounds: Inorganic	4.0	7.0	395,721	132,381
30	3. Prediction of Lung Cancer Rates by Sputum Cytology	0.2	0.0	35,000	42,644
33	4. Development of an Animal Model for Assessing Cofactors in Arsenic Associated Cancer	1.0	2.0	300,000	57,479
34	5. Histological Fingerprinting of Lung Carcinogens: Interdivisional Coordinated Studies	2.1	2.0	67,727	26,720
	B. Experimental	11.2	10.0	1,027,369	724,717
36	1. Toxicology of Industrial Tars	3.0	3.0	88,000	96,043
37	2. Pilot Study of Pulmonary Carcinogens in Smelter Dusts	0.8	1.0	53,000	88,499
38	3. Cocarcinogenic Potential of Fibrous Materials	1.5	1.0	300,000	24,486

Occ. Carcinogenesis Program Project No.	Activity & Project Titles	MY Efforts	Allocations Positions	Allocations Dollars	Obligations Dollars
39	4. Molecular Mechanisms in Occupational Carcinogenesis	0.4	0.0	92,382	123,834
40	5. Tissue Culture Studies Human Lung Fibroblasts	1.9	1.0	54,659	47,970
41	6. Pathogenicity of VC - Effect of Age and Exposure Duration	0.2	0.0	219,000	202,000
42	7. Mutagenicity and Carcinogenicity Testing of Chemicals by Use of Microbial Indicator Organisms	3.9	4.0	228,328	141,885
	III. Control	3.7	21.0	1,518,023	1,652,770
	A. Engineering (Evaluation & Control)	0	14.0	1,175,743	1,244,760
43	1. Respirator Research - Carcinogenesis		9.0	602,643	805,158
44	2. Engineering Control Criteria for Carcinogens		5.0	573,100	439,602
	B. Medical	0.0	0.0	0	0
	C. Technology Transfer	3.7	7.0	342,280	408,010
46	1. Carcinogen Training Program		2.0	108,000	99,600
47	2. Health & Safety Guides for Carcinogens	1.0	2.0	42,320	42,490
48	3. Carcinogen File Development	0.5	1.0	62,160	48,820
49	4. Develop Procedures for Documentation of Carcinogens (A Prototype Study)	1.5	1.0	100,000	185,000
50	5. Bladder Carcinogen: Information Transfer	0.7	1.0	29,800	32,100
		74.4	125.0	6,940,000	5,391,694

* Funding provided under the Interagency Energy Program

SUMMARY OF FIRST YEAR ACCOMPLISHMENTS

RECOGNITION

The first phase of NIOSH's recognition activity is surveillance. Using surveillance, recognition of problem areas is accomplished by:

- Structured studies or surveys involving development, modification, and utilization of data resources such as tumor registries,
- Evaluation of information acquired from sources such as official and other health and labor agencies, unions, individual workers, physicians, and medical centers, Occupational Safety and Health Administration, and the NIOSH Health Hazard Evaluation Program,
- Bioassay systems which utilize screening tests for identification of agents having carcinogenic potential,
- The acquisition of new entries to the Registry of Toxic Effects of Chemical Substances and the subsequent dissemination of the information.

Through the use of structured studies during FY 76, NIOSH attempted to identify occupational groups having an unusually high risk of developing cancer. It was found that leather workers had an unusually high risk for developing bladder cancer and consequently further review of cancer risks in the leather industry was undertaken. Also identified in these studies were excessive risks for bladder cancer among dairy farmers and for genital cancers among hairdressers and cosmetologists. In addition, a table was developed showing the relative risks of genital cancers for females employed in a variety of occupations.

An automated retrieval system for cancer mortality data has been developed using as one source of information cancer mortality data from the National Cancer Institute. These data have been utilized to 1) access death rates and Standardized Mortality Rates (SMR) for leukemia in counties with plants producing styrene-butadine rubber and 2) produce tables on mortality for selected cancer sites in countries identified with substantial numbers of persons employed in the leather industry. Also, a detailed report, prepared under contract, was published relating occupations vs. cause of death on approximately 300,000 Washington State males aged 20 or more years for 1950-1971.

In evaluating information gained from special sources, NIOSH completed two investigations of cancer clustering. One involved brain tumor cases at a steel mill in Wheeling, West Virginia, while the other was a follow-up mortality analysis of a chemical plant for the State of Maryland. Another cancer case involving possible clustering of pancreatic cancer in a chemical plant in Massachusetts is still underway.

After the surveillance phase recognizes a possible carcinogenic hazard by means described previously, assessment of the hazard is performed by means of:

- Development of Current Intelligence Bulletins
- Assessment of research and standards development priorities
- Assessment of gaps in knowledge.

The Current Intelligence System is a quick response mechanism which informs the occupational health community of new information on potential occupational health hazards. Unlike similar reports issued by other agencies, the Current Intelligence Bulletin presents all available information pertinent to the evaluation of a substance as a hazard in the workplace.

In January 1975, (following the vinyl chloride episode), NIOSH developed an information transfer mechanism to alert the occupational health community, including other government agencies, industry, labor, academia and public interest groups to previously unrecognized occupational health hazards. When new information on a potential occupational health hazard is received by NIOSH, it is researched as to its occupational health significance. At the same time, other interested Federal agencies are notified that NIOSH is evaluating the particular hazard with regard to its occupational health significance.

The information on the potential hazard is evaluated and supplemented by NIOSH. A background report is prepared defining the characteristics of the substance, including its toxicity in man and animal (e.g., carcinogenic potential), its production and uses, the number and type of workers exposed, and its possible impact on occupational health. Based on this evaluation, one of the following actions is taken:

1. The information is prepared for distrubution to NIOSH staff and key federal agencies only.
2. If the information warrants, a Current Intelligence Bulletin is prepared and sent to the general occupational health community and others as appropriate.
3. The information is deemed insufficient to warrant any further distribution by NIOSH.
4. Additional NIOSH research is recommended.

During FY 76 and the Transition Quarter, NIOSH alerted the occupational health community to the potential carcinogenic hazards of ethylene dibromide (in antiknock additives for gasoline and fumigants for grains and produce), chromate pigments (in paints, printing inks, and floor coverings), asbestos (in the servicing of brake and clutch assemblies), hexamethylphosphoric triamide (a laboratory solvent), biphenyls (a dielectric used in most electrical capacitors and some power transformers), chloroform (used to prepare fluorocarbons, as a multi-use solvent, and in numerous pharmaceuticals), and dimethylcarbamoyl chloride (used to produce certain pharmaceuticals). In addition,

briefing bulletins for twelve other potential carcinogens have been distributed to concerned federal agencies.

Assessment of priorities is determined by analysis of the severity of risk, and the type and extent of evaluation studies is determined by analysis of the information base gained through surveillance. Thus, in NIOSH planning, surveillance and assessment comprise the background information system and decision logic whereby NIOSH can develop projects to meet objectives in its carcinogenesis program. Accordingly, a substance identified to possess carcinogenic potential which would involve high risk to worker populations would be assessed to have a high priority; hence, a shift in resource utilization can be made toward evaluation and control. Conversely, a substance with low carcinogenic potential and slight risk in terms of potential for exposure would be assessed for lower priority and consequent minimal use of NIOSH resources.

In the area of priority setting and research analysis first year efforts were aimed at establishing an initial list of highest priority carcinogenic substances for further NIOSH review as special hazards. A working priority list of fifty-eight chemical substances was developed based on reported carcinogenicity evidence and data that were compiled relating to production, use, and occurrence. Bibliographies of pertinent world-wide literature were then prepared by contract for each substance. Seven of these substances were selected as candidates for prototype Hazard Review document development, and bibliographical citations were acquired. Five prototype documents are planned for development during FY 77. The Health Hazard Review documents will include summary evaluations of health hazard data and control recommendations that will offer some degree of protection to exposed workers. Active dissemination of these documents is planned through trade associations, professional societies, and labor unions.

After preparation of a Current Intelligence Bulletin or a Hazard Review, it often becomes apparent that gaps in knowledge exist to varying degrees. Often, a sampling and analytical method does not exist, and many times the existing methods need refinement before they can be used in an occupational setting. Other types of gaps in knowledge are in the disciplines of toxicology, epidemiology, behavioral science, control technology, etc. After analyses of the literature point to the presence of gaps in information, NIOSH conducts studies which will give the scientific community a better understanding of the nature of a particular carcinogen and how it should be controlled. The results of these studies serve as a tool for constantly updating and reassessing our priorities in the area of occupational carcinogenesis.

EVALUATION - INDUSTRYWIDE STUDIES

Industrywide epidemiologic research is performed, through longitudinal record studies and clinical/environmental field studies and surveys, to identify the occupational causes of disease in the working population and their offspring and to determine the incidence and prevalence of

acute and chronic effects from work related exposures to toxic and hazardous substances. The procedures that are utilized to conduct this industrywide research are outlined in the most recent edition of "The President's Report on Occupational Safety and Health." This research examines health hazards by two categorical groups: by industry and by agent.

During FY-76 and the Transitional Quarter, NIOSH had ongoing industrywide studies in the carcinogenesis area in the printing, dairy, uranium milling and mining, plywood, pulp and paper, coal gasification, phosphate fertilizer, aluminum, steel, antimony smelting, beryllium, cadmium smelting, pesticide formulator, and lead smelting industries. Ongoing agent studies included ionizing radiation, benzene, epichlorohydrin, fluorohydrocarbons, vinyl halides, styrene-butadiene, trichloroethylene, polychlorinated biphenyls, vinyl chloride, bis-chloromethyl ether, chloroprene, methyl chloride, benzyl chloride, asbestos and talc. Accomplishments included cohort selections, employee record microfilming, data coding, building of master files, and plant industrial hygiene surveys. Individual reports were prepared on all industrial hygiene surveys and walk-through surveys.

A selection of the industrywide studies that were ongoing in FY 76 and the Transitional Quarter are presented below in order to exemplify the epidemiological evaluation process.

1. Coal gasification is an alternate energy technology which is currently being explored for possible future use through several pilot plant operations, and when instituted will involve a substantial number of workers. The health effect on these workers from exposures found in this technology have not been well defined, although coal gasification processes involve many of the polycyclic hydrocarbons that are closely related to coke oven emissions which have been associated with an excess risk of lung cancer. The purpose of this industrywide study is to characterize these worker exposures and to define appropriate industrial hygiene and control technology practices that will be of use in reducing exposure levels. Four walk-through surveys were conducted of existing U.S. coal gasification pilot plants to provide technical insight into the technology. Based on this information, a contract was developed and awarded, in cooperation with the Energy Research and Development Administration and the Environmental Protection Agency, to conduct an industrial hygiene industrywide study of the technology.

2. In the steel industry, NIOSH research, through a contract, continued in the area of evaluating, through retrospective cohort mortality studies, the chronic health effects of working in the industry. Statistical tables portraying comparative mortality patterns by work area and cause of death were compiled for several cohorts of steelworkers. Specifically, mortality by work area tables were developed for: a) steelworkers employed in 1953 followed through 1970; b) steelworkers employed in 1961 followed through 1970; and c) steelworkers employed in 1953 followed through 1962, contrasted with steelworkers employed in 1961 followed through 1970. A doctoral thesis

was written utilizing the steelworker data base. The thesis described two methodological problems encountered in cohort studies of mortality related to industrial exposures, i.e., analyzing the separate effects of latency and duration of exposure and statistical consideration of competing causes of death. Detailed analyses of cancer mortality patterns within coke plants were prepared. Much of this material was presented at the OSHA coke oven hearings as the most up-to-date information on cancer risk associated with employment in specific work stations around coke ovens. A paper describing mortality patterns of steelworker retirees was prepared and accepted for publication in the Journal of Occupational Medicine. A paper describing comparative cause-specific mortality patterns among workers employed in the sheet and tin mill areas was published in the Journal of Occupational Medicine. A paper discussing the cause-specific mortality experience of men employed in the mason department of steel mills was submitted for publication in the Journal of Occupational Medicine. Detailed statistical tables were prepared showing comparative cause-specific mortality rates for men employed in foundry work and in the billet, bloom, and slab mills. A paper discussing the site-specific cancer experience of men employed in coke by-product and coal handling work areas of coke plants was published by the New York Academy of Sciences as part of the proceedings of the Conference on Occupational Carcinogenesis. In addition, the contract was modified to allow continuation of the examination of the mortality experience of the steelworkers by extending the follow-up period through 1975.

3. Animal studies have shown that when intratracheal doses of 3,4-benzo(a)pyrene (a known carcinogen) are administered with metallic antimony, more of the 3,4 benzo(a)pyrene is present than when given alone. Also, recent information from England indicates an increased risk from lung cancer for antimony smelting workers, specifically with antimony oxide production. These results indicate a need for further investigations into the risk of American workers who have experienced a much longer latent period since first exposure. To this end, a retrospective cohort mortality and industrial hygiene study was initiated. Walk-through surveys have been completed for the purpose of selecting a cohort to study and characterizing the antimony smelting industry. The cohort was selected (at one smelter), the detailed industrial hygiene survey completed, personnel records were microfilmed and coding of the personnel data initiated. The master file for the cohort is being established and the industrial hygiene report for use in identifying worker exposure classification, etc. is being prepared.

4. Several studies have shown the association between benzene exposures and damage to the haematopoietic system and development of leukemia. On this basis, a retrospective cohort analysis and industrial hygiene study of a cohort of U.S. workers having sufficient latency to demonstrate any chronic effects from benzene exposure was initiated. Complete literature searches were conducted; walk-through surveys, completed; and a cohort (two rubber plants) was selected. Also, the personnel records of the plants were microfilmed and coding of data was initiated. The

industrial hygiene portion of the study was delayed because of the rubber workers strike.

5. Bis-chloromethyl ether (BCME) is a potent lung carcinogen. While numerous studies are available to document this effect, data describing its formation or extent of occurrence in the occupational setting is minimal. Through the contractural mechanisms, NIOSH has been conducting an investigation of the possibility of BCME formation from the reaction of formaldehyde and ionic chloride compounds in selected work environments. To date the kinetics of the suspected reaction have been developed; walk-through and detailed industrial hygiene surveys, completed; and a final report is in preparation. Preliminary data indicate that the presence of reactants needed for BCME appeared in low ppm levels in textile finishing operations. No BCME was detected above 0.1 ppb in the textile environment using separate gas chromatography and gas chromatography/mass spectrometer analysis.

6. The present OSHA standards for talc exposure attempt to differentiate between the fibrous and non-fibrous varieties of talc and to account for free silica exposures. Different occupational hazards can be associated with the differing talc compositions, including the possibility of "biological inertness" for "pure talc;" however, the scientific evidence to support the adequacy for health protection by the present talc standards is not totally conclusive. Cross-sectional medical, retrospective mortality, and industrial hygiene studies are being conducted in an attempt to further determine if there is any excess risk of disease in talc workers, to determine a protective mass standard (in lieu of the present impinger standard) for non-fibrous talc, to characterize various commercial talc deposits in the U.S. as to asbestos and free silica content and to develop or evaluate analytical methods for talc in regard to asbestos content. To date, the industrial hygiene surveys of talc operations in New York and Vermont have been completed and reports are in preparation. The initial phases of the cross-sectional medical study of Vermont talc workers are complete and the mortality studies of New York and Vermont talc workers are to the stage where the master files have been developed and acquisition of death certificates has been initiated. One of the major NIOSH responsibilities during FY-76 in the talc area has been to provide assistance to OSHA in their continuing effort to enforce the existing talc standards against industry allegations that talc exposures are not causing adverse health effects in their workers and to identify which talcs actually contain asbestos. This assistance has amounted to many man-months of expert testimony, report preparation, etc.

7. Published studies on pesticide formulators have shown the need to evaluate the risk for chronic or long latency diseases such as cancer, kidney, and liver disease, hypertension-related diseases, and abnormalities of offspring. Existing studies are far from conclusive and because of the nature of the industry (i.e., potential high exposures among a large but dispersed population exposed), a retrospective mortality study to evaluate the potential for excess occupational disease was initiated. This study is being conducted through the

contractual mechanism and will consist of 1) determining the mortality status of approximately 5,000 workers who were employed as formulators for a minimum of 12 months prior to 1960 for 60 causes of death and 2) looking prospectively at a cohort of workers who were initially employed as formulators between January 1, 1960 and December 31, 1975.

EVALUATION - LABORATORY STUDIES

NIOSH evaluative laboratory studies in the carcinogenesis program are split into two groups, developmental and experimental. The developmental side is aimed at supporting NIOSH field studies and OSHA standards with practical monitoring, sampling, and analytical methods and with critical biological tests for identification of carcinogenic and co-carcinogenic hazards.

NIOSH efforts to develop and validate analytical methodologies has resulted in FY76 in the development of sampling and analytical methods for the following carcinogens, some of which are also shown as being the subject of a NIOSH Criteria Document: epichlorohydrin (Criteria Document), 4-4'-methylene bis (2-chloroaniline)(MOCA)(OSHA Standard), benzidine (OSHA Standard), and 3,3'-dichlorobenzidine (OSHA Standard).

A field kit to qualitatively measure the following carcinogens which are OSHA Standards has been developed with a prototype currently being validated: 4,4'-methylene bis (chloroaniline)(MOCA), benzidine, 3,3'-dichlorobenzidine, 1-naphthylamine, 2-naphthylamine, 4-aminobiphenyl, 4-nitrobiphenyl, and n,n-dimethylaminoazobenzene.

The NIOSH method for arsenic has been assessed for its precision and detection limits at the level of the present OSHA Arsenic Standard. Research to develop sampling and analytical methods for the following is presently being conducted and will continue in FY 77: 2-naphthalene, 1-naphthalene, ethylene imine, ethylene oxide, beryllium, and nickel carbonyl.

New applications of instrument methodologies have been developed for chrysotile and other contaminants: X-ray diffraction analyses of chrysotile collected on filters has been shown to be feasible. Bulk samples of chrysotile have been analyzed using differential thermal analysis, and an instrument is being developed to analyze multiple elements.

Much of NIOSH's carcinogenic methods development has necessarily been performed outside of NIOSH by interagency agreement with the Energy Research and Development Administration and by contract. NIOSH laboratory facilities in Cincinnati have not been considered safe enough for handling such hazardous materials. However, design of a NIOSH carcinogen laboratory at the Ridge Avenue Facility in Cincinnati has been completed and most of the necessary equipment has been obtained. It is hoped that delays in construction of this much needed laboratory can be overcome so that more in-house work can be initiated in FY 77.

Significant FY76 accomplishments in the area of biological methods development are limited to progress in developing a method of histological fingerprinting of lung carcinogens and in developing an animal model for assessing cofactors in arsenic associated cancer. In attemping to develop histological fingerprinting of lung carcinogens, it was shown that in uranium miners, undifferentiated small cell tumors were most characteristic as contrasted to epidermoid and adenoid types among smokers. However, epidermoid and adenoid types were increased in incidence also, but to a lesser extent. The large cell undifferentiated type was not increased. An initial study of workers exposed to arsenic at a copper smelter showed an excess of poorly differentiated epidermoid carcinoma. Work was begun on a similar analysis of cancer among three other populations of arsenic exposed persons.

Efforts to develop an animal test system (or model) that is responsive to the induction of cancer by inorganic arsenicals are in support of a laboratory project described below to identify pulmonary carcinogens in smelter dusts.

Inasmuch as other agencies such as NCI, NIEHS, FDA, and EPA have moderate to strong programs in biological experimentation programs, this form of research in the evaluation process of the NIOSH carcinogenesis initiative necessarily exhibits a lower profile than would ordinarily be expected in a research oriented institute. Bioassay programs for mass, routine screening of chemicals for carcinogenic potential are avoided. Similarly, development and use of in vitro screening tests in NIOSH are held to a minimum insofar as routine testing programs are concerned. These are being addressed by other agencies.

Accordingly, emphasis in NIOSH's experimental biological research is designed and directed toward elucidation of occupational carcinogenesis as applied to interactions among agents of priority interest in the occupational environment. Whenever possible the laboratory experimental programs complement and add to our understanding of unexplainable trends indicated by surveillance and field epidemiology. In this connection, it is becoming clear that there is a need for experimental studies which employ the inhalation route of exposure for mammalian species. However, because inhalation studies are so expensive, there must be judicious selection of agents and experimental protocol as well as genuine effort in coordination between research groups in government, industry, and academia.

During FY 76 the subjects of NIOSH's experimental biological research were industrial tars, smelter dusts, fibrous materials, and vinyl chloride.

The project on the toxicology of industrial tars provided for the extension of studies, begun in FY'72, on the toxicity of coal tar. The toxicity data developed in this study will provide a basis for the assessment of hazards associated with exposure to organic emissions from asphalt roofing, coking, and related industrial processes.

Previous work performed under the project has shown that the primary biologic response to coal tar is one of skin tumorigenesis, but it is yet to be determined which components of the complex mixture elicit this response. It has been established that the neutral components of coal tar evoke the production of skin tumors, characteristic of squamous cell carcinomas. However, the identification of the carcinogens is desirable to assess the occupational hazard of any particular sample on a quantitative basis. The work for FY 76 included continuation of the in-house screening tests for biologic activity of tar neutral subfractions by the mouse-skin bioassay, and completion, except for histologic evaluation, of the coal tar inhalation exposure studies with multiple species of animals.

The purposes of the project to define the factors influencing carcinogenicity of smelter dust and arsenic are to identify one or more of the inorganic compounds in dusts from copper and lead smelters that are responsible for the induction of lung cancer and to develop an animal test system that is responsive to the induction of cancer by inorganic arsenicals. Smelter dusts, before and after physical separation procedures, were injected intratracheally into animals and the incidence of lung cancer will be correlated with the concentration of the dust's constituents; e.g., lead, arsenic, antimony, cadmium, copper, nickel, and other inorganics.

Arsenicals have been implicated as etiologic agents in the induction of skin and lung cancer for over 50 years, but the experimental animal evidence to date has not demonstrated that pure arsenicals cause cancer. One of the probable reasons is that the animal test systems used were not sensitive enough. In developing an animal test system for testing arsenical carcinogenesis, a special rat diet was formulated with respect to vitamins and minerals. Certain rat groups are receiving a similar diet with low concentrations of magnesium and alpha-tocopherol (vitamin E). It has been shown that magnesium deficient diets can induce lymphosarcomas. The arsenicals are administered simultaneously via the animals' drinking water, and the incidence of carcinogenic response (leukemias/tumors) is being evaluated.

In previous experimental animal studies on the co-carcinogenic potential of fibrous silicates, it was found that chrysotile asbestos was a much more potent co-carcinogen than a carcinogen; i.e., as a co-carcinogen for benzo-a-pyrene, chrysotile produced a three-fold increase in tumor incidence and a five-fold increase in tumor size. In the same experiments chrysotile alone was not tumorigenic. In FY76 studies were performed to determine the smallest amount of chrysotile needed to potentiate benzo-a-pyrene after intrapleural injections. In addition, other minerals, including crocidolite asbestos, fiber glass, talc, and quartz, are being tested for their co-carcinogenic potential in the same test system. The solubilities and surface areas of these minerals are also being measured and related to their co-carcinogenic potentials. To date, chrysotile, at all doses tested (10, 1, and 0.1 mg), potentiated the carcinogenic effect of benzo-a-pyrene; none of the other minerals tested potentiated the benzo-a-pyrene. The results of

these studies will help us better understand and more adequately control cancer risks attributable to these materials.

Studies of molecular mechanisms in occupational carcinogenesis include an hypothesis that predicts the cations and classes of organic compounds that are essential for cancer. Briefly, the hypothesis predicts that cancer can follow the binding of divalent cations (specifically divalent cations of Hg, As, Te, Pt, Be, Tl, Cd, and Os) to the N3 and N9 nitrogens of purines and to specific classes of organic compounds forming 4-membered, highly stable complexes, which are then incorporated into DNA. A number of these divalent cations are proven or suspected carcinogens that are frequently encountered in the work place. A contract entitled "Formulation and Stabilities of Chemical Complexes of Beryllium and Platinum" was negotiated with the Illinois Institute of Technology in June 1976. Anticipating successful synthesis of the desired complexes, it is planned that these same complexes will be injected into mice to test their carcinogenicity. They will also be tested with one or more of the in vitro mutagenesis testing systems.

Inhalation exposures of rats to 1,000 ppm of vinyl chloride were begun in June 1976 under contract and will continue to October 1977. The purposes of the study are to (1) determine the effect of exposure duration on the incidence of vinyl chloride induced lesions, (2) define the histologic alterations that can be used to predict the development of vinyl chloride induced tumors, (3) determine the effect of age of the animal on the incidence of induced lesions, and (4) determine the usefulness of some clinical tests in the diagnosis of vinyl chloride induced lesions in rats. Derived data are considered essential for development of a complete criteria document on vinyl chloride and for an understanding of the chemical's induction of carcinogenesis.

After completion of a literature survey to determine the present knowledge of interaction of carcinogens and other physical and chemical agents, a study was designed to determine the effect of heat exposure on the incidence and growth rate of benzo-a-pyrene induced tumors. A contract was awarded to the Ohio State University to carry out the laboratory work. The study will be accomplished in three phases. Initially the exposure facility will be defined as to its physical characteristics of temperature and humidity (4 weeks). Secondly, animal exposures will begin (52 weeks). Finally an 8-week period has been alloted for data reduction and analysis.

CONTROL

Efforts to develop engineering controls for carcinogenic substances emphasize development of improved respirator types and improved process control in the handling of carcinogens.

Evaluations have begun for respirator sorbents for vinyl chloride and arsine and respirator filters for arsenic trioxide and for contaminants

in a coke plant. Sorbent testing is expected to be completed in FY 77 contingent upon the completion of NIOSH's Cincinnati carcinogen laboratory facilities.

A draft of an amendment to 30 CFR Part 11, Respiratory Protective Apparatus-Tests for Permissibility, was prepared. This amendment would provide new performance requirements for dust, fume, and mist respirators and thereby improve the protection for workers handling carcinogenic materials where airborne concentrations require use of respirators.

The control technology assessment program for carcinogens has begun with an assessment of light machining operations for determination of the adequacy of controls. Additional control technology projects are planned for FY77 implementation in the roofing, welding, brasing (of nickel), foundry, smelter, and drycleaning industries. These projects are being developed in coordination with a larger NIOSH control technology initiative for control of noncarcinogenic hazards as well as carcinogenic hazards. A work plan for control technology assessments of industries and major processes utilizing carcinogenic materials will be completed in the second quarter of FY78.

Technology transfer projects in the NIOSH carcinogenesis program are intended to translate the information developed in the previously described research projects into understandable and useful information for labor and industry. Such end products as the Registry of Toxic Effects of Chemical Substances, criteria documents, Health and Safety Guides, training films, training courses, etc., all exemplify a type of effort NIOSH has sponsored in past years, but not always with an impact specifically identifiable with a thrust toward cancer prevention. The carcinogenesis program will alleviate this shortcoming. Accordingly, such a program should incorporate those program areas involving education by means of appropriate information dissemination, e.g. publications, demonstrations, training, and interaction with other government agencies with responsibility for detection, health care delivery, or prevention.

Active technology transfer projects during FY76 included development of a carcinogen training program, Health and Safety Guides for Carcinogens, a carcinogen file (or registry), and special procedures for preparation of criteria documentation for carcinogens.

As a better understanding of the potential of carcinogenic hazards is gained by the occupational health community, a corresponding awareness is more slowly gained by industrial management and the labor force. However, this awareness is gained with difficulty and considerable misconception. Even in the case of a proven human carcinogen, it may be difficult to consciously draw a relationship between long term, low level exposures to a colorless, odorless substance and the appearance of a malignant tumor twenty or thirty years in the future. A better understanding of such hazards may be conveyed by educational programs, publications, and films. For several years, NIOSH has developed these materials for safety and noncarcinogenic chemical hazards. As a final

step in developing training programs specifically for carcinogenic hazards, NIOSH is presently collecting and assembling information from all existing sources. Contacts have been made with secondary and university teachers, state science supervisors, and professional societies to monitor their activities. Some training film prepared by by the American Chemical Society have been obtained.

NIOSH is also working with OSHA and the National Cancer Institute (NCI) to develop a mass audience education film on the problems of occupational cancer. An interagency agreement between OSHA and NCI calls for NIOSH assistance in this work. NIOSH has assisted OSHA in its contract with George Washington University to develop the above-mentioned mass audience films, and NIOSH training personnel reviewed proposals in response to NCI's request for contract proposals, "Safe Handling of Chemical Carcinogens in the Laboratory."

Development of a Health and Safety Guide for Carcinogens was initiated in FY76. The proposed format will consist of one booklet, consisting of two major sections:

Section I will be employee oriented. It will discuss training, regulated areas, work practices, protective equipment, etc. It will translate Federal Register language into an easily comprehended library style with many pertinent illustrations to amplify the text. This section will be suitable for separate printing for distribution to employees.

Section II will be directed toward the technical management team of the employer. It will discuss engineering controls, recordkeeping, medical surveillance, and other legal requirements. The language will be more technical than the first section, but should be comprehensible to a non-specialist. Illustrations will also be used to amplify the presentation.

The first draft will be directed toward the 14 regulated carcinogens described in Section 1910.1003 thru 1016 of the OSHA Regulations. It will be subsequently modified, if possible, to incorporate asbestos, vinyl chloride, and cancer suspect agents.

On June 23, 1975, a request was placed in the Federal Register for any information on the 1,500 suspected carcinogens then listed in the NIOSH Registry of Toxic Effects of Chemical Substances. An information storage and retrieval system was to be established to organize this information. However, the response to the request was so limited that this was unnecessary. Therefore new strategies for obtaining the needed information were developed. As described above in the "Recognition" section, a literature search was made on the fifty-eight carcinogens for which information was needed immediately.

During FY 76 and the T.Q. a total of thirty-three recommended standards were transmitted to the Occupational Safety and Health Administration. Of these, twenty-seven were new criteria documents, five were revised recommendations on previously issued criteria documents, and one was a recommendation for an emergency standard on kepone. Seven of the thirty-three recommended standards identified carcinogenicity as a potential health effect. Those were for benzene, beryllium, carbon tetrachloride, chloroform, chromium, isopropyl alcohol, and kepone. For all of these with the exception of isopropyl alcohol, the most current recommendation for an environmental standard was based on carcinogenic potential of the chemical rather than some non-carcinogenic toxicity. In the case of isopropyl alcohol, the carcinogenic hazard is associated with a possible cancer threat in the manufacturing process rather than with isopropyl alcohol itself. The recommended standard provides for special precaution in the manufacturing process.

PROBLEM AREAS

As mentioned previously, the NIOSH carcinogenesis program amounted to $1.8 million before and $6.9 million after the expanded Occupational Carcinogenesis Program. This is a dramatic and necessary increase. It was anticipated that such an increase would be accompanied by "start-up" problems. These problems, which include personnel hiring lag and delays inherent in government contracting procedures, were planned for even though the additional funds and positions were not available to NIOSH until February of 1976. However, other unplanned difficulties have been encountered.

Since the passage of the Occupational Safety and Health Act, NIOSH has depended heavily on contract work. In this first year of the expanded Occupational Carcinogenesis Program contract work is even more important. Experienced personnel could not be hired into all carcinogenesis positions early enough to accomplish significant, reportable tasks. Rather than waiting until positions could be filled, many projects were initiated in part by contract. Normally contract work can be quite satisfactory though considerably more expensive than in-house work. In the case of industrywide studies of the printing industry and of epichlorohydrin use, contract work has been delayed by a legal problem. Certain employers are of the opinion that while NIOSH may have right of entry, its contractors do not. To avoid this problem proposed regulations were published in the Federal Register in June 1975. The proposed regulations were modified considerably after public comment and sent to the Secretary of HEW in April 1976. They were not promulgated during FY 76 or the Transition Quarter and work on the contract projects mentioned was delayed.

Other difficulties center about NIOSH's facility problems. For several years, NIOSH has conducted subacute, long-term animal studies in its laboratory at 1014 Broadway St., Cincinnati. These were modest but meaningful studies. More extensive studies, especially those involving highly hazardous substances, were performed on contract or by interagency agreement because the 1014 Broadway laboratory was not suitable. In the Spring of 1976, NIOSH began moving its laboratories to the Taft Center. At the same time, design was completed for an animal inhalation laboratory for carcinogenic substances to be constructed in the garage area of Taft Center. But because we had not secured the deed for the Taft Building from the Environmental Protection Agency, we were unable to proceed with the renovation of the garage area. Since that time, new animal inhalation studies have not been initiated, and schedules for ongoing studies in the Broadway facility have been readjusted so as to end all studies by December 31, 1976. At present, NIOSH has the necessary personnel to perform inhalation studies and is lacking only a facility. Delays in construction of this facility will delay inhalation studies on short asbestos fibers, perchloroethylene, and trichloroethylene.

One difficulty in establishing any carcinogen laboratory is that ventilation controls are critical. Ventilation in most buildings and

laboratories including the Taft Center maintains rooms at positive pressure with respect to the outside. Carcinogen work areas should be maintained at negative pressures to prevent escape of carcinogenic substances, and exhausted air must be disposed of by appropriate means separate from all other ventilation. Therefore, the animal inhalation facility will be constructed in the garage area of the Taft Center where existing ventilation is not a factor. A special ventilation system will be installed to service this area alone. In the Ridge Avenue facility in Cincinnati, existing positive pressure ventilation creates a similar problem. However, this will be solved by considerably modifying an area that now has conventional ventilation. Serious sampling and analytical methods development could not be accomplished at the Broadway facility because ventilation was totally inadequate. In order to accomplish badly needed work in 1974, NIOSH entered into an interagency agreement with the Atomic Energy Commission (now a part of the Energy Research and Development Administration) to develop sampling and analytical methods for several of the 14 carcinogens which were the subject of an OSHA emergency standard. AEC's Los Alamos Scientific Laboratory, which is operated by the University of California, modified one of its laboratories at a cost of $75,000 to meet necessary standards for carcinogens. Obligations for this project through FY 76 have reached $750,000. Had proper laboratories been available inhouse, NIOSH could have performed the same work at approximately one-half the cost.

FY77 PLANS AND PROSPECTS

Despite the difficulties experienced above the NIOSH Occupational Carcinogenesis program has gained considerable momentum as can be seen by comparing figures for FY76 and T.Q. funds allocated and obligated. While NIOSH had allocated $6,940,010 for the Program in FY76, only $5,391,694 were obligated. However, if Transition Quarter allocated and obligated figures of $2,713,o00 and $3,584,623 are annualized for comparison, allocated and obligated rates would be $10,852,000 and $14,338,492 per year respectively. Even if the $1 million dollar expenditure for construction of a carcinogen laboratory is deducted, T.Q. allocation and obligations rates were at $6,852,000 and $10,338,492 per year. For FY77, NIOSH has allocated $10.7 million dollars for the Occupational Carcinogenesis Program which is roughly equivalent to T.Q. non-contruction expenditure rates (TABLE IV). NIOSH looks forward to support of this program by the National Cancer Institute in the amount of $3 to $4 million.

Legal problems encountered with contract industrywide studies should be resolved for FY77 since regulations covering these projects were promulgated early in October of 1976.

With the awarding of a contract for the construction of the new high hazard carcinogenic chemistry laboratory NIOSH should be able, by Spring of 1977, to begin to develop inhouse the necessary sampling and analytical methods for monitoring carcinogens. It has also been reported that we can expect to receive the deed for the Taft facility in late October. This will allow us to move forward in the construction of an animal inhalation facility and in initiating inhouse inhalation toxicological research.

TABLE IV

NIOSH Carcinogen Allocation - FY 77

Activity	ManYears	%	Dollars	%
I. Recognition	23.6	19.7	1,151,000	10.8
A. Surveillance	7.4	6.2	488,000	4.6
B. Assessment	16.2	13.5	663,000	6.2
II. Evaluation				
A. Industrywide Studies	60.1	50.3	4,446,300	41.5
1. Studies by Industry	9.3	7.8	730,200	6.8
2. Studies by Agent	50.8	42.5	3,716,100	34.7
B. Laboratory Studies	25.0	20.9	3,980,200	37.2
1. Developmental Res	14.4	12.0	1,930,300	18.0
2. Experimental Res	10.6	8.9	2,049,900	19.2
III. Control	11.0	9.1	1,121,700	10.5
A. Engineering	6.0	5.0	940,600	8.8
B. Medical	1.0	.8	21,100	.2
C. Technology Transfer	4.0	3.3	160,000	1.5
	119.7	100	10,699,200	100